Learning to appreciate others: neural development of adopting other people's mental perspectives

Thesis
presented to the Faculty of Arts
of
the University of Zurich

for the degree of
Doctor of Philosophy

by

Mengia Dosch
of Tinizong-Rona GR

Accepted in autum semester 2008
on the recommendation of

Prof. Dr. rer. nat. L. Jäncke
Prof. Dr. med. E. Martin

Fabian Thadeus
Men & Renata

Summary

Human beings are social beings. One crucial prerequisite for successful interaction is the ability to reason about other people's mind and understand other people's mental and emotional states. Social neuroscience has recently started to investigate the neural mechanisms underlying our capacity to represent other person's mental states and emotions. Neuroimaging studies in adults have thoroughly investigated brain regions that are recruited when another person's perspective is taken (taking a third person's perspective as compared with taking one's own perspective). Despite the remarkable results from neuroscientific research in adults, very little has been done so far to explore the development of perspective taking in children and adolescents. The aim of the first study was to investigate the development of the neural network that yields cognitive perspective taking in school-aged children and adults. We therefore developed a task requiring the appraisal of leisure activities form a third- and first-person perspective. The results revealed that adults were more efficient than children during the perspective taking task, whereas both groups were concordant and equally appropriate in their judgments. Brain imaging data indicated that the development of perspective taking is associated with changes in brain activity within the described neural network of social cognition involving posterior parietal (mainly the inferior parietal cortex) as well as prefrontal brain areas (mainly the right dorsolateral prefrontal cortex). We have been able to specify that neural development of perspective taking accompanies a shift in brain activity from frontal to posterior and from bilateral to left unilateral parietal brain activation. We further tested, by means of variance measures and signal change of neural activity, whether increased efficiency during development is supported by a focalization of the neural network. The results indicate that the additionally activated right inferior parietal cortex in children did not show more inter-subject variability than the other brain areas. Thus we can conclude that children use a qualitatively different, but coherent network in order to reason about other persons mind.

The focus of the second study was to investigate the neural network underlying cognitive perspective taking at the onset of puberty. In addition, we were interested in developmental differences between pubescent girls and boys. Behaviorally, children, adolescents and adults did not differ in appreciating 3PP. Despite of this equivalent performance, we found quantitative gender and age-group differences in reaction times for 3PP versus 1PP judgments. Moreover, by recording brain activity with fMRI, we observed differences between males and females as well as between age-groups in the activated fronto-parietal neural network. Processing a 3PP activated predominately the previous described fronto-parietal network across children, adolescents and adults. The data of the second study show a different developmental pattern for boys and girls. We observed that pubescent girls and boys significantly differed in their proficiency of perspective taking (△RT) as well as in their neural activation patterns. Increased efficiency in female was characterized by a decrease in activity in the right dorsolateral prefrontal cortex. This was not the case in males. In males, increased efficiency was related to changes in laterality within the in the inferior parietal cortex. These results warrant the conclusion that neural development of social cognition differs between male and female, which is particularly striking during adolescence.

The present PhD thesis had the aim to deliver novel answers and questions for further investigation. The results of these two studies provide new evidence that perspective-taking ability continues to develop after childhood and is associated with neural changes in the fronto-parietal network. Moreover, the results highlight gender-specific neural development of cognitive perspective taking during puberty.

Zusammenfassung

Menschen sind äusserst soziale Wesen. Die Fähigkeit, die Gedanken, Gefühle und Absichten anderer Menschen zu verstehen stellt die Grundlage einer erfolgreichen sozialen Interaktion dar. Um mentale Zustände anderer Menschen verstehen und antizipieren zu können, benötigen wir grundsätzliche die Fähigkeit zwischen eigenen und mentalen Zuständen anderer Personen zu unterscheiden. Darüber hinaus müssen wir in der Lage sein, unabhängig unserer eigenen Perspektive (1. Person-Perspektive, 1PP), die visuell-räumliche oder mentale Perspektive anderer Personen einzunehmen (3. Person-Perspektive, 3PP). Mit Hilfe bildgebender Verfahren konnten neurowissenschaftliche Studien zeigen, welche Hirnregionen aktiviert sind während Probanden sich in eine andere Person versetzen und deren Perspektive einnehmen. Während einige Studien an Erwachsenen die neuronalen Grundlagen der Perspektivenübernahme untersucht haben, ist die Entwicklung dieser Fähigkeit sowohl in Verhaltensstudien als auch in neurowissenschaftlichen Studien kaum untersucht.

Die vorliegende Dissertation liefert einen ersten Ansatz zur neurowissenschaftlichen Untersuchung der Entwicklung der mentalen Perspektivenübernahme bei Kindern und Adoleszenten mittels funktioneller Magnetresonanztomographie. Die erste Studie beschäftigt sich mit der Entwicklung der neuronalen Netzwerke, die mit dem Prozess der Perspektivenübernahme assoziiert sind. Die Resultate zeigen, dass Kinder und Erwachsene die Perspektive einer dritten Person qualitativ übereinstimmend und adäquat einschätzen. Quantitative wird de 3PP mit zunehmendem Alter effizienter (kürzere Reaktionsseiten im Verhältnis zur Verarbeitung der eigenen Perspektive) beurteilt. Neurologisch ist die Entwicklung der Perspektivenübernahme mit Veränderungen der neuronalen Netzwerke im fronto-parietalen Kortex assoziiert. Dabei zeigte sich eine Entwicklung von frontaler zu posteriorer und von bilateraler zu unilateraler parietaler Hirnaktivierung. Die zunehmende Effizient der Perspektivenübernahme zeichnet sich weiter durch eine Fokalisierung der neuronalen Netzwerke aus. Die Resultate der ersten

Studie lassen den Schluss zu, dass Kinder qualitativ verschiedene, aber kohärente neuronale Netzwerke benutzen während sie sich in den mentalen Zustand einer anderen Person versetzen.

Die zweite Studie hatte zum Ziel, die neuronalen Netzwerke der Perspektivenübernahme zur Zeit der Pubertät zu untersuchen. Dabei galt das Hauptinteresse möglichen entwicklungsbedingten Geschlechtsunterschieden. Dazu wurden Kinder, junge Adoleszenten und Erwachsene beider Geschlechter untersucht. Wie die erste Studie bereits zeigte, unterscheiden sich die Altergruppen in der 2. Studie in der qualitativen Beurteilung der 3. Perspektive nicht voneinander. Auch hier wurden Alterseffekte bezüglich der Reaktionszeiten für die 3PP im Vergleich zur 1PP beobachtet. Zusätzlich zeigen sich Unterschiede zwischen den Geschlechtern. Die Geschlechts- und Altereffekte widerspiegeln sich auch in den Hirnaktivierungsdaten. Die Verarbeitung der 3PP aktiviert das bereits beschriebene fronto-parietale Netzwerk bei Kindern, Adoleszenten und Erwachsenen. Es zeigen sich allerdings unterschiedliche Entwicklungsmuster für Mädchen und Knaben. Die zunehmende Effizienz der Perspektivenübernahme ($\triangle$RT) ist bei Mädchen mit einer Abnahme der Aktivierung im rechten dorsolateralen präfrontalen Kortex assoziiert. Diese Abnahme zeigen die Knaben nicht. Bei Knaben ging die zunehmende Effizient der Perspektivenübernahme mit einer Veränderung der Lateralität im inferioren parietalen Kortex einher. Die Resultate der zweiten Studie lassen die Schlussfolgerung zu, dass die Fähigkeit zur mentalen Perspektivenübernahme sich nach der Kindheit weiter entwickelt. Darüber hinaus scheint sich die Entwicklung – insbesondere während der Adoleszenz - zwischen den Geschlechtern zu unterscheiden.

Acknowledgement

First of all I would like to thank Prof. Dr. Ernst Martin-Fiori for giving me this great opportunity to work on my favorite topic. I would like to thank him for his mentoring and the possibility to use and benefit from the perfect infrastructure of the MR-Center. I specially appreciate his tolerance and confidence in me.

My special thanks go to Thomas Loenneker for the enormous technical support and motivation in difficult situations, and to Peter Klaver for the fruitful discussions and his scientific guidance. My gratitude also goes to Prof. Dr. Lutz Jäncke for giving me the opportunity to complete this thesis.

Furthermore, I'd like to express my greatest thanks to my colleagues at the MR-Center Dr. Kerstin Bucher, Dr. Karin Kucian, Beat Werner, Sanne van der Mark for their help and encouragement, and especially to Janine Lichtensteiger and Stephanie Rotzer for clarifying discussions when I was doubting.

My deepest thanks go to Fabian and my parents who always believe in me and support what I do.

1 Introduction

1.1. Social Neuroscience

Social neuroscience can be defined as the exploration of the neurological underpinnings of social behavior and cognition (Decety et al., 2006). Social neuroscience investigates psychological constructs such as empathy, decision-making, moral reasoning or perspective taking that are difficult to map directly onto neural processes. It is therefore challenging to set ecological valid social situation to explore complex and dynamic relationship between the brain and social interactions in the laboratory.

The notion that behavior has a biological bases goes back to at least Galen in the ancient Greece who suggested that our social nature is influenced by an admixture of four substances in our body, called the four humors (blood, black bile, yellow bile and phlegm) that were linked to personality and interpersonal styles (sanguine, melancholic, choleric phlegmatic). Although humorism has long since fallen out of research interest, the notion that the material body, including the brain contributes to psychological processes has become increasingly important in psychological research. Of particular interest to social neuroscience is the famous patient Phineas Gage. After the incredible survival of an accident in which an iron rod penetrated his frontal brain, his personality and social functioning was changed so much, that his friends said he was "no longer Gage" whereas his motor skills and cognitive abilities retained. This case provided the first evidence that damage to the frontal brain can affect social behavior and personality. In the following, other cases of neurological damage have demonstrated the neural contribution to successful social functioning. For instance damage to a certain region of parietal cortex can lead individuals to feel as if other people are controlling their bodily movements. Damage to the fusiform gyrus may cause an inability to recognize faces even though other object can be recognized. Taken together, neurological case studies have been

extremely important for the fundamental understanding of the relationship between brain and behavior, but such cases are rare and thus are not sufficient to sustain a new area of research.
The accessibility of functional magnetic resonance imaging technology in the early 1990s enabled researchers to investigate cortical and subcortical brain bases of behavior in healthy normal volunteers. Since many cognitive psychologists became cognitive neuroscientists, they first investigated the neuronal bases of language, memory and attention. Since the beginning of this century social neuroscience started to capture attention of researchers from multiple disciplines such as cognitive neuroscience, social psychology, developmental science, economics, and cognitive psychology. Currently, social neuroscientist investigate automatic and controlled aspects of social cognition, mental state attribution (also known as theory of mind), empathy, decision-making, moral reasoning but also self-knowledge, self-recognition and self-awareness. Many of these topics are in its infancy with no more than a handful studies intending to identify brain regions that are involved in the process of interest. The most obvious impact of neuroimaging methods for social neuroscience is that they provide tools to disentangle cognitive and emotional processes, which experientially feel similar and produce similar behavioral results, but actually rely on different underlying mechanisms. And, on the other hand, it could be shown that different processes such as perceiving and observing physical pain rely at least partly on same brain mechanisms.
A drawback of social neuroscience is that it can be perceived as the comeback of phrenology (Uttal et al., 2003). Functional imaging has become a very popular and in many respects also a seductive tool leading to over-simplistic characterization of social cognition and behavior. Although most neuroscientist agree that it is impossible to determine whether a person is experiencing empathy or anger by just looking at the activity in particular brain regions, several neuroscientist seem to neglect that knowledge, particular when labeling brain areas as the "the empathic brain" or specifying brain regions as being responsible to psychopathological behavior. It is clear; on one hand our social behavior is in many respects specialized for guiding our

social interactions with others and that it is more complex than other aspects of behavior. But on the other hand, it is equally apparent that social cognition depends on many of the same mental processes and hence presumably on many of the same brain structures as non-social mental processes. One therefore might argue that studying social cognition requires somewhat different methods. Since neuroscientists use constructs such as empathy for which we cannot provide precise definitions, findings of single studies may not permit decisive conclusions. In contrast to studies investigating perceptive processes, it is likely to be that every single study on social cognitive information processing investigates only a particular aspect of social cognition which is limited by its in eliminable confounds but consistency of activation across many studies may will permit reliable statements of brain-behavior relationship.

1.2. Top-down and Bottom-up Processes of Understanding Other Human Beings

The ability to understand other person's emotions and mental states is essential for virtually all aspects of social behavior. Understanding other's emotional and mental states requires both rapid stimulus-driven processes as well as reflective top-down processes (Decety et al., 2004). Evidence for stimulus-driven mechanisms of understanding others initially came from imaging studies showing that the same motor regions are activated during the execution and observation of specific movements (Gallese et al., 2004). Subsequent studies showed that direct experience and observation of pain or emotions such as disgust activates overlapping neural systems. It has thus been argued that shared neural representations facilitate the direct experiential understanding of affective states which in turn might provide a substrate of empathy (Decety & Jackson, 2004; Keysers et al., 2004; Wicker et al., 2003). However, understanding others is not always so simple. Under certain conditions, context information is needed to constrain differentiated attributions about other person's intentions and emotional states. Furthermore, the automatically activated shared representations and presumable empathic connections might be inhibited –if one perceives for instance another person to be a potential unfair competitor or if the nonverbal cues of emotions are ambiguous (Singer et al., 2006). Therefore the engagement of controlled processes enables us to actively adopt another person's perspective and thus understand more complex emotional and mental states when stimulus-triggered processing of situational information is not sufficient. These processes in turn depend on different neural network (Olsson et al., 2008).

In everyday language as well as in scientific literature the bottom-up processes of understanding others are referred to as empathy and the top-down processes as theory of mind, mentalizing, and cognitive perspective taking. Although all of these concepts describe our ability to step into the 'shoes' of others, the capacity to 'mentalize' and to 'empathize' are distinct and rely of different neuro-cognitive circuits.

The focus of the present PhD-thesis was the investigation of the development of the top-down process of understanding others, in particular the development of cognitive perspective taking and its neural underpinnings. In the following, the term social cognition will be used to summarize different social cognitive aspects such as perspective taking, mentalizing, theory of mind, which often are used as synonyms.

1.3. Stepping into Other Person's Shoes: the Ability of Perspective Taking and its Development

The ability to take another person's perspective is crucial for successful social interaction. Reasoning about others, and understand what they think, feel or believe involves stepping into their 'mental shoes' and thus adopt their perspective (Gallese et al., 1998). Perspective taking includes the awareness of one's own subjective space or mental state (first-person perspective or 1PP) and the ability to ascribe locations, mental states or emotions to another person (third-person perspective or 3PP).

There is currently much debate about the mechanisms of perspective taking. How do we automatically switch roles from oneself to another person in everyday social interaction? A predominant view is that we understand others by mentally simulating their actions (Harris, 1995). Neurophysiological studies have supported the 'simulation theory' demonstrating that common brain areas are activated both when we execute a certain action and when we observe another person performing the same action (this is known as the mirror neuron system) (Decety et al., 1997). The discovery of the mirror neuron system has further supported the simulation theory. In the following it has been suggested that simulating another person's action is a ontogenetic precursor of understanding thoughts and emotions (Gallese & Goldmann, 1998). On the other side of the debate the 'theory-theory' claims that we use a common sense of psychological theory of folk psychology to understand other people's mind, rather than internally simulating them (Gopnik et al., 1997).

Piaget has first described the development of children's perspective-taking abilities. He claimed that children are cognitively egocentric. They do not know that they are mental entities with conceptual, perceptual and affective perspectives and points of view. As a consequence, they cannot know that they themselves have their own perspective and these perspectives can differ from those of others. Therefore they unwittingly respond in terms of their own point of view when asked to respond in terms of another person's point of view. Piaget believed that children become less egocentric with age, but he did not claim that adults are wholly non-egocentric in their thinking (Piaget, 1959). Furthermore social psychological studies with adults have demonstrated that even adults frequently make predictable error when assessing other persons' perspectives (Gilovich et al. 2002, Nickerson 1999, Royzman et al. 2003).

The tendency to use self-knowledge as the primary basis for developing a model of what others know has been described by several authors as a default mode of reasoning about others' mind. Although the details and the level of complexity of the task used to assess this ability in children and adults may vary, it seems that both have difficulties in setting aside their own privileged knowledge in predicting another persons' perspective. Consistent with Piaget's view, several studies since the 1950s have documented increasing perspective taking abilities with age (Flavell, 1992).

A second wave of research on the development of children's knowledge about the mind of others started in the 1980's and is still dominant in the field of cognitive developmental psychology: the theory of mind research. The term "theory of mind" originally comes from primate research. Premark and Wood ruff (Premack et al., 1978) published a paper with the title: does the chimpanzee has a theory of mind? It refers to the question, whether chimpanzees have an implicit assumption that the behavior of others is determined by their thoughts, desires, beliefs and attitudes. In the following year's developmental psychologists began to investigate the development of a theory of mind (ToM) in children, by testing them if they can predict another persons behavior based on that person's false belief (Wimmer et al., 1983), for review see (Flavell, 1999). This second wave of research have shown that signs of social competence develop during early infancy, when infants start to ascribe actions to an entity by the age of 12 months (Johnson, 2003; Spelke et al., 1995). At the age of 18 months infants begin to understand intentions and they acquire joint attention skills, for example, to follow an adult's eye gaze toward a goal (Carpenter et al., 1998). These early social abilities precede higher social skills such as "the false belief understanding". By the age of 4-5 years children start to realize that another person's belief about a particular situation may differ from their own (what has been called: "theory of mind") (Astington, 1993; Baron-Cohen et al., 1985; Gopnik, 1993). More complex is the comprehension of a 'faux pas' situation. A 'faux pas' happens when somebody says something she/he should not have said. Understanding 'faux pas' requires simultaneous representation of two mental states: the perspective of a person, who commits the 'faux pas', and the representation of a second-person's perspective, who may feel offence or irritation. 'Faux pas' may not be reliably understood before the age of 9-10 years. Baron-Cohen could further show that females precede males in 'faux pas' detection (Baron-Cohen et al., 1997).

Taken together, large literature has accrued on the development of social competence during infancy up the age of 6 years but very little has been done so far on later development. Baron-Cohen pointed out that the passing of the standard theory of mind tests should be considered as relatively early points in the development of social competence rather than the end-point.

1.4. Perspective Taking and the Brain

The first researchers who started to investigate the neural bases of social cognition using brain imaging methods were inspired by developmental psychology (Flavell, 1999; Fletcher et al., 1995; Frith et al., 2003). Theory of mind paradigms were used to investigate the neural mechanism of social cognition by comparing brain activation while participants reason about another persons belief with conditions requiring them to understand physical causal reasoning. A meta-analysis on theory of mind imaging studies (Frith & Frith, 2003; Gallagher et al., 2003) revealed a consistent involvement of mainly three brain regions: the medial prefrontal cortex, the posterior superior temporal sulcus extending to temporo-parietal junction and the temporal poles – the so-called "mentalizing network". The problem, however, with using ToM paradigms is that they use physical conditions to contrast the ability to represent mental states. It thus remains open to what extend the self perspective is involved in modeling someone else's perspective. To accommodate for these problems another line of research starts to investigate the neural mechanisms underlying the ability to represent mental states of others. These studies compare conditions in which participants imagine another person's perspective with condition in which they imagine their own perspective. The focus of those studies was to investigate whether taking someone else's perspective as opposed to taking ones own perspective relies on overlapping or differential brain mechanism. Taking a third-person perspective, whether it involved thinking about how another person would think, feel or imagine them making an action relative to one's own perspective has been associated with brain activation in the inferior parietal cortex, the medial posterior cortex (posterior cingulate/precuneus) and medial prefrontal cortex (David et al., 2006; Jackson, Meltzoff et al., 2006; Lamm et al., 2007; Ruby et al., 2001, 2003, 2004; Vogeley et al., 2001). Furthermore neuropsychological evidence has additionally pointed out the importance of the inferior parietal cortex (IPC) and TPJ for perspective taking as well as for the distinction between self and other (Decety et al., 2003). Damage to this regions not only impairs the ability to represent different perspectives (Samson et al., 2004) and it can lead a patient to believe that his own body is controlled by external forces (Mesulam, 1981). In summary, perspective taking studies in adults have shown common brain activation in 1PP and 3PP conditions as well as differential activity between the two perspectives. It has been suggested that the differential brain activity implies that simulation cannot be the only mechanism involved in mental state attribution.

2 Developmental Brain Plasticity

Neuroimaging techniques have shown that the human brain undergoes substantial developmental changes from infancy though adolescence (see Paus, 2005 for review). These developmental changes do not follow rigid rules whereby different developmental phases are initialized by genetically determined programs. Brain development is based on maturation and neuroplasticity, which refers to the lifelong ability of the brain to reorganize neural circuits based on experiences or sensory stimulation. Plasticity is the mechanism for emerging competence and skill acquisition, and allows the brain to adopt itself to its environment. In order to learn and improve new skills, there must be persistent functional changes in the brain that represent new abilities (Elbert et al., 2001). Brain plastic changes occur at multiple levels of neuronal organization, from molecules and synapses to cortical maps and neural networks (Buonomano and Merzenich, 1998). The brain mechanisms underlying plasticity are based on adjustments in the strength of connections between brain cells, reflected by alterations in the internal structure and number of synapses.

The early brain development is characterized by rapid brain growth (Garey, 1984). The proliferation and overproduction of neurons occurs prenatally, whereas cell death (apoptosis) begins and continues until the second postnatal year. Likewise, an overproduction of cell arborization and synaptic contacts can be observed in the first year of life, which then is followed by an elimination of 'pruning' phase (Huttenlocher, 1990). During synaptic pruning the unused and infrequently used connections are eliminated. Connections that have been activated most frequently are preserved, a mechanism referred to as Hebbian competition (Hebb, 1949). Experiences determine which connections will be strengthened and which will be pruned. The importance of postnatal experience for normal development has first been described by several animal studies. For instance Hubel and Wiesel demonstrated that the brain of cats undergoes sensitive periods during which environmental stimulation is crucial for normal brain development and perceptual development (Wiesel et al., 1963). These experiments suggested that human brain might show the similar sensitive periods in very early development. Only later post-mortem brain research by Huttenlocher demonstrated that some human brain areas continue to develop beyond the early childhood.

Today, non-invasive magnetic resonance brain imaging techniques (MRI) allow the analysis of living human brains and furthermore provide the opportunity to investigate human brain development across life-span by longitudinal studies. Most MRI studies have focused on developmental changes in grey matter volume (which correspond to the volume of cell bodies, synapses and neuropil) and white matter volume (which correspond to the volume myelinated axons). Their findings are remarkable consistent (Giedd et al., 1999; Gogtay et al., 2004; Paus, 2005; Sowell et al., 2003).

The volume of white matter increases during the first 20 years of life. While the sensory and motor regions become fully myelinated in the first few years of life, axons in frontal and parietal regions continue to be myelinated into adolescence (Giedd, 1999). In contrast, grey matter volume development appears to follow a non-linear pattern. The peak of grey matter density and the following experience-dependent pruning processes are regionally specific. Grey matter in the frontal and parietal lobe increases during childhood with a peak at about age 12 years followed by a decline. Grey matter volume in the temporal lobe reaches its peak only by the age of 16 years, whereas cortical grey matter in the occipital lobe continued to increase after the age 20 years.

Moreover, the region-specific developmental decrease in GM volume which has been reported in frontal, parietal and temporal areas (Giedd et al., 1999; Gogtay et al., 2004; Sowell et al., 2004; Sowell et al., 2002; Wilke et al., 2007) differs between boys and girls. The changes in frontal and parietal cortices occur one to two years earlier in boys than boys. In this context it has recently been suggested that the development of the adolescent brain might respond differently to changing levels of testosterone and estradiol. E.g. it could be demonstrated that the levels of sex steroids in children between 8 and 15 years of age were associated with sexual dimorphic gray matter areas (Neufang et al., 2009). The reported neuroanatomical changes during adolescence may reflect a refinement of neuronal connections that could be related to cognitive and emotional development.

Giedd (1999) has demonstrated that the development of grey matter volume is different in males and females at least in some regions. Grey matter density in the frontal lobe increases during pre-adolescence with a maximum in 11 years old females and 12 years old males followed by a decline during post-adolescence. Parietal grey matter development follows a similar pattern, with a peak of volume at the age of 10 years in females and at 12 years in males. Temporal and occipital grey matter development was not different between girls and boys. Although no measure of puberty rather than levels of steroid hormones were taken, it might be argued that the onset of puberty rather than age per se triggers these gender-specific time courses of development at least in frontal and parietal regions.

2.1. Implications to Functional Brain Development

The continued myelination is thought to influence the transmission speed of neural information whereas the relatively late elimination of excess synapses has been suggested to be responsible for more diffuse and widespread activation pattern and less efficient cognitive strategies in children and adolescents (Casey, Tottenham et al., 2005; Durston & Casey, 2006a). Previous functional neuroimaging studies in children and adolescents reported that development is supported by changes in pattern of brain activation, including enhancement of activation in critical regions, attenuation in others, and changes in the extent of activation as well as shifts in lateralization (Durston & Casey, 2006b). While the nature and time course of structural changes during development have been described in detail, its relation to the development of the functional development is, however, not yet clear.

3 Analyzing the Brain: Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is beside event-related brain potential recordings (ERPs) based on the scalp recorded electrical signals of the brain the most widely used method for studying the neural basis of human behavior. fMRI provides us the opportunity to study the interplay between brain and behavior and since the method is non-invasive the investigation of children's brain function is possible. FMRI is based upon the principles of nuclear magnetic resonance (NMR), a technique that is sensitive to the magnetic properties of molecules. The fMRI technique is capable to visualize the physiological changes in oxy- and deoxyhemoglobin concentration in cortical venous blood vessels, in particular the capillary bed, upon neuronal activation. The fMRI signal depends on the fact that there is a close coupling between changes in activity of a neuronal population and changes in its blood supply. Since fMRI can monitor focal changes in hemodynamic parameters, it provides only an indirect measure of neuronal activity. The basic mechanism underlying fMRI is the blood oxygenation level -dependant (BOLD) contrast (Ogawa, Lee et al. 1990). Since the magnetic susceptibility of deoxyhemoglobin is greater than that of oxyhemoglobin, MRI signal is sensitive to the ratio of deoxy- to oxyhemoglobin. The increase in blood supply triggered by increases in neural activity delivers more oxygen than is needed to meet metabolic demands. Therefore, the blood draining from an active neuronal population is more richly oxygenated than during the resting state. In consequence the ratio of deoxy- to oxyhemoglobin concentrations decreases, which leads to an increase in the MR signal. Contrasting both active and resting states reveals areas of neuronal activation. Thus, fMRI is able to detect changes in neuronal activation between different states. The basic procedure to localize brain areas related to a specific function is to manipulate the experimental parameters over time and then to interrogate the hemodynamic signal changes in each volume element (voxel) in the brain in relation to the experimental manipulation. As a result, statistical activation map are generated, showing in which voxels in the brain signal changes correlate best with the changes in the experiment.

3.1. Functional Brain Imaging in Pediatric Population

The noninvasive technique of fMRI is considered to be an ideal technique to study brain functions in children. Despite the enormous advantages one has to act with several problems when working with children. Many aspects of participating in an fMRI experiment can be challenging for children (e.g., assessment in a medical environment, large and noisy equipment and confinement in a small space). Discomfort with the scanning procedure may affect performance and neural activation through decreased attention to instructions, decreased task performance and engagement of emotional and stress-related systems during the procedure. Explanation of, and acclimation to, the scanning environment prior to the actual fMRI data acquisition, is key to avoiding these problems. It has to be ensured that the child understands the task and is physically able to operate the devices. Moreover, the child has to be willing and cooperate during the whole experiment (30 minutes) in the uncomfortable scanner environment without substantial head movement. Simulation of the scanner experience allows the child to get used with the procedure. We used a teddy bear to simulate and explain the procedure to the children and after that, the child could play the investigator by moving the bear in and out of the scanner. Scanner noise not only interferes with cognitive tasks it also hampers children’s comfort. For noise reduction we used earplugs and additionally equipped the inside of the scanner with a sound diminishing foam mat. The wearing of video goggles helped children to not actually realize that they are being moved into a narrow hole. To keep the child occupied during the localization and anatomical scans a video was shown.

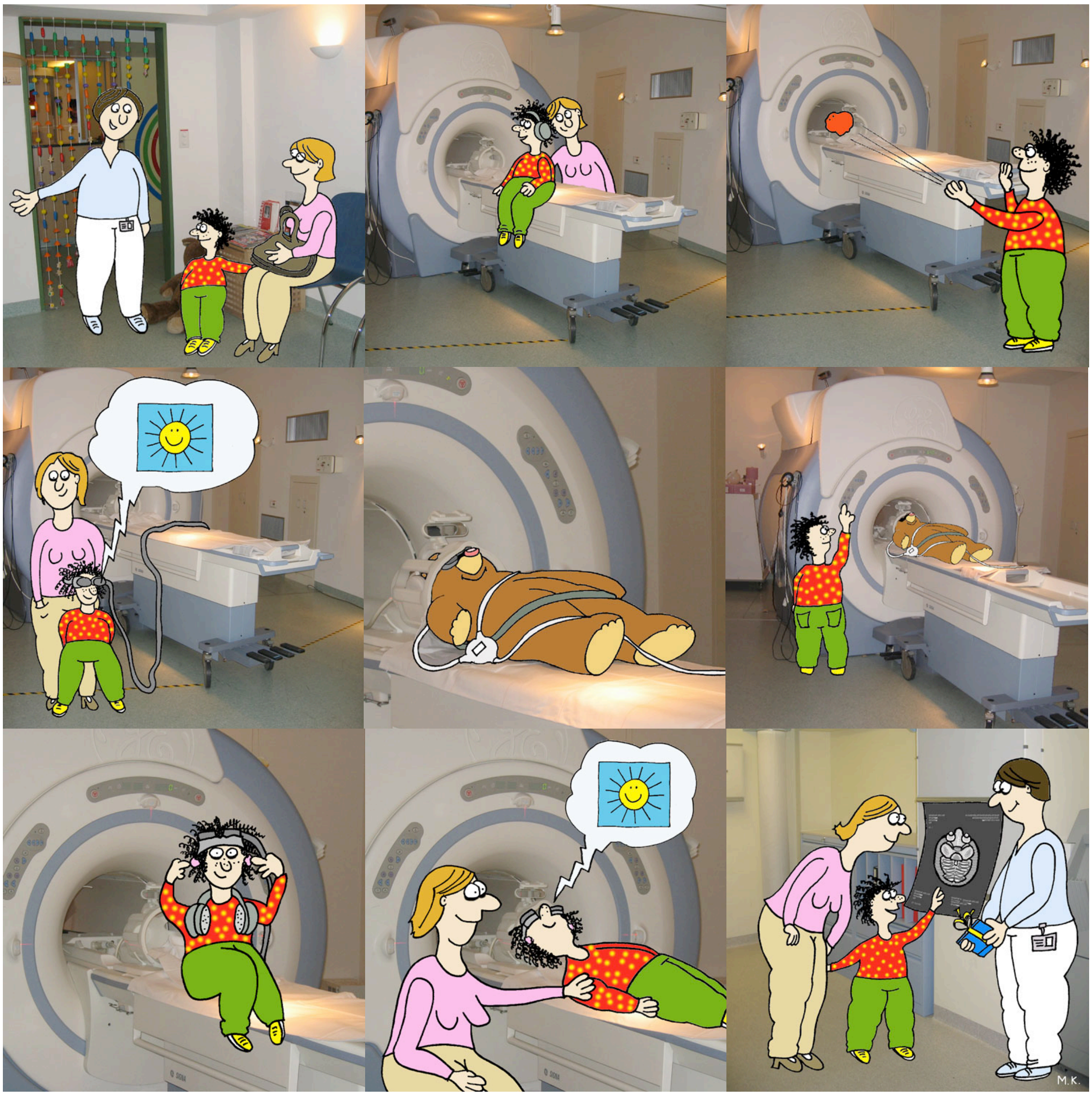

Figure 1 : The comic being used in order to explain the scanning procedure to the child

4 Conclusions and Hypothesis

Despite the remarkable results from neuroscientific research on perspective taking abilities in adults, little has been done so far to explore the neuronal development underlying these functions in normal achieving children and adolescents. No study has investigated the neural development of cognitive perspective taking yet but a handful fMRI studies investigated other social cognitive processes such as understanding irony (Wang, 2006), thinking about intentions (Blakemore, 2006) or social-knowledge retrieval. Among theses studies there seem to be some consistency regarding the direction of change in prefrontal cortex activity. In various frontal regions a decrease of brain activity with development was found, particularly in the medial prefrontal and the inferior prefrontal cortex. On the other hand structural brain developmental studies have revealed changes in grey matter volume during late childhood, adolescence and even early adulthood (Giedd et al., 1999; Gogtay et al., 2004; Sowell et al., 2003; Toga et al., 2006). It is currently unknown how brain maturation influences the development of social cognition. A general idea coming from studies on development of language and executive functions is that children show similar but more distributed neural pattern compared to adults. These findings have been referred to as focalization of neural development (Casey, Galvan et al., 2005; Durston, Davidson et al., 2006). A problem, however, with interpreting focalization of neural activation is that differences in brain activation between children and adults can be confounded with differences in variability between group.

Aims of Study 1: To investigate the behavioral and neural development of cognitive perspective taking and to test whether the development of perspective taking is supported by a focalization of the neural network by means of measures of variance and signal change of neural activity.

Hypothesis of Study 1: we hypothesize that processing another person's perspective would become increasingly efficient during development (decrease of reaction times) and is associated with changes the fronto-parietal network of social cognition involving posterior parietal regions (mainly the inferior parietal cortex) as well as prefrontal brain areas.

We further tested whether the development of perspective taking is supported by a focalization of the neural network involved in perspective taking by means of measures of variance and signal change of neural activity.

Aims of Study 2: Structural brain developmental studies in adolescence have not only demonstrated that grey matter development is prolonged but also revealed that the brain undergoes considerable gender-dependent development during adolescence (Giedd 1999). The gender-specific development is especially pronounced in parietal and frontal brain regions. The aim of study 2 was therefore to investigate perspective taking at the onset of puberty in girls and boys.

Hypothesis of Study 2: Given the facts that 1) brain imaging studies on perspective taking in adults have identified the importance of a fronto-parietal network, 2) structural studies demonstrated that these regions continue to develop until early adulthood and 3) differ between girls and boys; we hypothesize developmental differences in the neural network underlying cognitive perspective taking between genders.

5 Learning to appreciate others: Neural development of cognitive perspective taking[1]

Dosch M, Loenneker T, Bucher K, Martin E, Klaver P

5.1. Abstract

Neuroimaging studies in adults have thoroughly investigated brain regions that are recruited when we put ourselves in another person's shoes. Taking a third-person perspective (3PP) as opposed to a first-person perspective (1PP) has been associated with brain activation in the inferior parietal cortex, the medial posterior cortex and the prefrontal cortex. Here we investigate for the first time the development of the neural network that yields cognitive perspective taking. Twelve adults (aged 25-32 years) and twelve school-aged children (aged 8-10 years) were investigated using functional magnetic resonance imaging (fMRI). Behaviorally, we found a decrease of reaction time differences between 3PP and 1PP with age indicating that adults were more efficient in processing a 3PP. Despite the reaction time differences both groups were equally accurate in their judgments. Brain imaging data indicated neural activity in the left inferior parietal cortex and precuneus for adults during 3PP as compared with 1PP judgments. Children additionally showed enhanced activity in the dorsolateral prefrontal cortex and the right inferior parietal cortex. We found a significant interaction between groups and brain activation in the right dorsolateral prefrontal cortex and in the right inferior parietal cortex. These results suggest that the development of the ability to reason about another person's mind accompanies a shift in activity from frontal to posterior brain regions and from bilateral to unilateral left inferior parietal cortex.

---

[1] Artice in Press, *NeuroImage* (2009), doi:10.1016/j.neuroimage.2009.12.013

5.2. Introduction

Since the beginning of this century neuroscience methods have been applied to the investigation of social cognition in adult subjects. Reasoning about other people's mind and understanding what they think, feel or believe requires the ability to step into their "mental shoes" and reason according their perspective (Gallese et al., 1998). This is crucial for successful social interaction. Perspective taking includes the awareness of one's own subjective spatial and mental space (first-person perspective, 1PP) and the ability to ascribe visuo-spatial perspectives and mental states (cognitive or emotional states) to another person (third-person perspectives, 3PP). In the present study we investigate the ability to take another person's mental perspective.

Neuroimaging studies revealed brain regions that are active when we step into another persons mental perspective to represent his or her experience as compared to one's own. For instance, we take a 3PP when we try to appreciate what another person thinks about a particular topic or feels in a given situation. Taking the mental perspective of another person, as opposed to the own perspective has been associated with brain activation in the inferior parietal cortex, including the temporo-parietal junction (TPJ), medial posterior cortex (posterior cingulate/precuneus) and medial prefrontal cortex (David et al., 2006; Ruby et al., 2001, 2003, 2004; Vogeley et al., 2001). Furthermore neuropsychological evidence has also highlighted the importance of the inferior parietal cortex (IPC) and TPJ for perspective taking as well as for the distinction between self and other (Decety et al., 2003a). Direct cortical stimulation of the right IPC has induced the phenomenon of out of body experience in an epileptic patient (Blanke et al., 2002), and damage to this area can lead a patient to believe that his own body is controlled by external forces (Mesulam, 1981).

Despite the remarkable results from neuroscientific research on perspective taking in adults, little has been done so far to explore the neuronal development underlying these functions in normal achieving children. Structural brain developmental studies have revealed changes in grey and white matter during late childhood, adolescence and even early adulthood. Both cross-sectional and longitudinal studies demonstrated that changes in frontal and parietal regions are especially pronounced and prolonged. Whereas white matter volume seems to increase linearly during the first two decades of life, grey matter development, particularly in posterior parietal and prefrontal cortices, increases from early childhood until about the age 12 (around the onset of puberty) and is followed by a decline during adolescence (Giedd et al., 1999; Gogtay et al., 2004; Sowell et al., 2003; Toga et al., 2006). While the nature and time course of structural changes during development have been described in detail, few studies focused on functional development. A general idea coming from studies on development of language and executive functions is that children show similar but more distributed pattern compared to adults. These findings have been referred to as focalization of neural development (Casey et al., 2005; Durston et al., 2006).

It is currently unknown how brain maturation influences the development of social cognition. Most research on the behavioral development of social cognition has been conducted in children between the age of 4-7 years (Astington, 1983, Baron-Cohen, 1993, Leslie, 1985), which indicates that major steps in social cognition are completed by that age. Although no study has investigated the neural development of perspective taking abilities, a handful fMRI studies investigate other social cognitive processes such as understanding irony (Wang, 2006), thinking about own intentions (Blakemore, 2006) or social-knowledge retrieval (Pfeifer, 2007). Among these studies, there seems to be some consistency with respect to the direction of change in prefrontal activity. In various frontal regions a decrease of activity with development was found particularly in the medial prefrontal and the inferior frontal cortex (for review see (Blakemore, 2008).

Hence, on the basis of these structural and functional imaging results we hypothesize that the neural development of cognitive perspective taking is associated with changes in brain activity within the described neural network of social cognition involving posterior parietal regions (mainly the inferior parietal cortex) as well as prefrontal brain areas.

To test this hypothesis we developed a task requiring the appraisal of leisure activities from a third- or first-person perspective. Leisure activities are much more self-defining during childhood and adolescence than school activities because they provide more opportunity for self-direction and initiative than school performance activities. Self-defining activities tell children and adolescents something about "who they really are" or "what they are like" as a person and are therefore essential for the distinction between oneself and other persons (Larson, 2001). During the task short statements of real life situations were presented to both adults and children, who were required to make judgments for themselves and for another person who was introduced by a story. To assure that especially children adopt the mental perspective of another person and to keep the level of familiarity equal across all participants we chose a very different and unknown personality as a third-person. Choosing a third-person with very different characteristics allowed us to provoke qualitative differences between 1PP and 3PP judgments. To introduce participants with the other person we used a story of a child/adult with autistic behavior- we called him Paul. The story comprised his social behavior at home and during kindergarten and school time, his academic skills as well as his special interests. Participants did not know that Paul has been diagnosed as having Asperger's syndrome nor did they know any other psychiatric diagnosis.

Since brain imaging as well as lesion studies on perspective taking in adults pointed to the importance of a fronto-parietal network, and structural studies showed that this network is not fully developed until early adulthood we expected that processing another person's perspective would become increasingly efficient during development (decrease of reaction times) and is associated with changes in brain activation within the prefrontal (particularly in the medial and inferior frontal) and the inferior parietal cortex. We further tested whether the development of perspective taking is supported by a focalization of the neural network involved in perspective taking by means of measures of variance and signal change of neural activity.

5.3. Methods

Participants

Data were acquired from 12 children between 8.5 and 10.6 years of age (mean 10.0 years, 6 male) and 12 adults (aged 24.6-32.3, mean 29.1, 4 male). All children were recruited from public schools in the city of Zurich. Participants completed the German version of the autism-spectrum quotient questionnaire for adults or for children (AQ, Baron-Cohen, 2006) – a quantitative self-report instrument for assessing how many autistic traits a person has. None of the participants scored above the critical minimum of 30 out of 50 autistic traits (mean children: 18.73, mean adults: 16.35). No significant group differences ($t(1,21)$=-1.19,p=0.249) or sex differences were found ($t(1,21)$=0.187, p=0.854). Participants were also asked to indicate on an analogous scale (ranging from 0-100) how much they felt like Paul irrespective of sex. Female and males did not differ in their ratings (mean female=193, mean male=254, t(1,22)=0.904, p=0.376). Adult participants were university students. Four additional children had to be excluded due to extensive movement during the fMRI scanning (>5mm) and were therefore also excluded from behavioral analysis. All participants were right-handed as assessed by the Edinburgh Inventory Scale (Oldfield, 1971). None of the participants had a significant history of medical, psychiatric or neurological disorders on the basis of self- or parent-report. None of the participants used any neurotropic or psychotropic medication. Written informed consent was obtained from all participants, as well as written informed parental consent for child participants. The study was approved by the local ethics committee and conducted in accordance with the guidelines set out in the Helsinki Declaration.

Task Description

Children were introduced to a virtual “other child” by reading a story about Paul a child with autistic behavior; adults likewise learned about a grown-up person with autistic behavior. During the fMRI measurement, the task required participants to make judgments about 32 leisure activities for themselves or for the other person. Activities with and without social interaction (with SI, no SI) were chosen to provoke differences in judgment for the 1PP and 3PP condition (assuming that Paul would dislike all social interactions). Separate task versions were created for children and for adults. The task employed a design in which the type of stimulus and the perspective taken by the participants were manipulated. In the self-perspective condition, subjects were asked to evaluate how much they like to do certain activities. In the other-perspective condition, subjects were instructed to imagine Paul and answer according to his preferences and interests and to ignore their own. In all trials, subjects were presented first with a picture of themselves or of Paul (duration 2 seconds) to indicate the perspective they had to adopt for answering the upcoming question. Subsequently, a sentence (e.g. ‘going to a friend’s birthday party’ or ‘reading a book’) was presented in black on a grey background (duration 6 seconds) together with a slider for answering, followed by a fixation cross (500 ms). Sixteen null-events in which only a fixation cross was shown were included and presented randomly. Participants were required to make their judgment by pressing the left or right button with the middle or index finger of their right hand. The button press moved a red marker on a slide on a continuous scale from left “I don’t like to do this activity at all” to right “I like to do this activity very much” (the scale range was from -100 to +100 with no visible scale in between). The longer the left/right button is pressed, the more the slider moves to the left/right side of the scale. The starting point of the red marker on the continuous scale was presented randomly. Each of the four conditions (1PP with SI, 1PP no SI, 3PP with SI, 3PP no SI) consisted of 16 trials which had to be judged according to both perspectives (total 64 trials). The sequence of the trials was generated randomly for each participant. Each activity had to be judged for themselves as well as for Paul.

Experimental Procedure

Before the scanning session we took a picture of the participant and introduced him/her to Paul by showing a picture of him. Then, participants were instructed to learn about the other Paul by reading a story about a male child/adult with autistic behavior describing his social behavior, academic skills as well as his interests. Participants did not know that Paul has the diagnosis of Asperger Syndrome.

We used different versions for adults and children. The difference between histories was that Paul's biography continued until adulthood for adults, but stopped at childhood (ca. 10 years) for the children. Similarly, the photograph of Paul was adapted to the age of the participants. The story comprised 200 words for children and 293 for adults. Participants were then asked to retell the story and answer several questions to ensure that they understood correctly and could imagine the Paul's personality. After introducing participant to Paul we carefully instructed them in the whole fMRI procedure and explained the task. Participants then practiced 5 trials from the 1PP and 5 from the 3PP. We again emphasized that it was very important to really try to imagine Paul and that we were interested in seeing how their brain works while they are thinking of him. We used MR-compatible video goggles to present the stimuli and additional acoustic noise protection by headphone (MRI Audio/Video System, Resonance Technology, Inc., USA) throughout the examinations. The task was programmed by Cogent implemented under MATLAB (http://www.vislab.ucl.ac.uk/CogentGraphics/).

MRI Data acquisition and analysis

BOLD sensitive images were collected on a 3.0 T General Electric MR-scanner using a gradient-echo EPI-sequence with a repetition time of 2000 ms and a 64x64 matrix. Altogether, 32 slices were aligned to the anterior and posterior commissure (flip angle = 50º, FOV= 24cm, slice thickness per volume = 3.8mm, 360 repetitions). Secondly, a three dimensional T1-

weighted anatomical scan (FOV = 230 mm x 198 mm x 158 mm, matrix = 224x192x132; TR = 8.6 ms; TE = 2.1 ms) of the whole brain was acquired. Images were analyzed using SPM5 (Statistical Parametric Mapping software, Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm). The fMRI data were realigned and un-wrapped for movement correction and were then normalized to a SPM template with a resampled voxel size of 3 mm^3 and smoothed with a Gaussian kernel (full width at half maximum: 9mm).

For each participant the expected hemodynamic responses for each trial were modeled by two response functions, which were a canonical hemodynamic response function (HRF) and its temporal derivative. The functions were convolved with the event train of stimulus onset to create covariates in a general linear model. Misses were modeled as a parameter of no interest. Parameter estimates for four conditions (1PP with SI, 1PP no SI, 3PP with SI, 3PP no SI) were obtained by maximum-likelihood estimation while using a temporal high-pass filter (cut-off 128 s) and modeling temporal autocorrelation as an AR(1) process. Since neural development of perspective taking (1PP, 3PP) was the focus of our interest, we collapsed trials with and without social interaction. We added the analysis of the brain activation associated with the type of task (with SI, no SI) in the supplementary material.

In a voxel based analysis comparison between each condition and rest, and direct comparison between conditions were thresholded at $p<0.05$ (FWE corrected, $k>10$) and $p<0.005$ (uncorrected, $k>5$ voxels) for regions for which we had a strong a priori hypothesis, namely, the pre-frontal and parietal cortex (Forman, 1995, Pfeiffer, 2007). To specifically look at developmental effects of perspective taking we calculated a ROI analysis on the basis of the activation patterns from the main effect of 3PP and 1PP judgments. Because we have two independent groups the ROIs were based on the activation patters across all participants (3PP > 1PP and 1PP > 3PP with a threshold of $p=0.005$, uncorrected, $k>5$ voxel). The children's and adults' data were compared in 12 regions of interest (ROI). According to these main effects

10-mm spheres around the local maxima of each significant cluster for each contrast (3PP>1PP and 1PP>3PP) were created using marsbar (http://marsbar.sourceforge.net/). Mean percent signal changes were taken from the raw data of every study participant for all conditions and activated voxels. For the contrast 3PP>1PP the following coordinates were taken to generate ROIs: left inferior frontal cortex (x=-42 45 0), right dorsolateral prefrontal cortex (middle frontal gyurs) (x=39, y=24, z=27), left inferior parietal cortex (x = -36, y = -57, z = 39), right precuneus (x=6, y=-69, z= 39), and right inferior parietal cortex (x=39, y=-48, z=45) . For the contrast 1PP>3PP the following coordinates were taken to create ROIs: left posterior cingulate cortex (x=-3. y=-33, z= 42 and x=-6, y=-54, z=21), anterior cingulate cortex (x=0, y=15, z=-6), left medial prefrontal cortex (x=-9, y=48, z= 9), left middle frontal cortex (x=-24 y=39 z=39), left superior parietal lobule (x=-27, y=-87, z=42), right parahippocampal gyrus (x=36, y=54, z=0) and left middle temporal gyrus (x=-57, y=-66, z=21). For statistical analysis we used a repeated measure ANOVA with the within-subject factor perspective (1PP, 3PP) and the between-subject factor group (children, adults) for each ROI. To look after the potential effect of similarity between participants and Paul on brain responses, we correlated the ratings obtained from the participants with each ROI.

To examine whether the differences between children and adults in brain activation are caused by maturation rather than by performance differences in reaction times between groups, we separated the groups in good and bad performers. Using the median of reaction time performance for 3PP-judgments in both groups we built four groups. Thereafter brain activity within each ROI was analyzed using a repeated measure ANOVA with perspective (1PP, 3PP) as within-subject factor and age (adults, children) and performance (good-performer, bad-performer) as between-subject factors.

Current techniques of data analysis (e.g. SPM random effect second-level analysis) allow the identification of common areas of brain activation within a population. Since higher inter-individual variability is a principle characteristic of a developing population, we compared intersubject-variability of brain activation between children and adults. To visualize the inter-subject variability in location of brain activation we build probability maps in each group. A probability map is a measure of the spatial consistency of brain activation and shows how many subjects activated a particular voxel (Xiong et al., 2000). This technique allows for the identification of activation that is missed by group averaging and indicates what portion of the study population contributes to the overall group. To calculate the probability map for each group, we used one-sample T-maps for the contrast 3PP>1PP from each participant (threshold $p<0.05$, uncorrected). Using MRIcroN (http://www.sph.sc.edu/comd/rorden/mricron) we built the color scale that represents the percentage of subjects who activated for each voxel (ranging from 15%-100%). To further analyze the variability of brain activity, we estimated the nearest local maxima for each ROI-coordinate in each subject and calculated the standard deviation along the x-, y-, and z-coordinates of each group. The nearest individual local maxima had to be within the left parietal cortex for the ROI in the left inferior parietal cortex, the left and right precuneus for the ROI in the precuneus and in the right parietal cortex for the ROI in the right inferior parietal cortex. Otherwise it was excluded from analysis. Euclidean distance values *d* around the mean location (x_0, y_0, z_0) for each selected ROI were also calculated for each subject using the following equation

$$\sqrt{\ } (x_i-x_0)^2+(y_i-y_0)^2+(z_i-z_0)^2$$

where x, y, and z are coordinates in MNI space for each individual (i). The Mann-Whitney *U*-Test was used to test for group differences in each ROI ($p<0.05$), because it is insensitive to the assumption of independence of each coordinate. It is also more robust against violations of a normal distribution of population.

5.4. Results

Behavioral Data

Judgments

Figure 2a shows the participants' judgments for the four conditions. With the selection of activities with and without social interaction (with, no SI) we provoked differences in judgment for self and other conditions. The results (Figure 1) show that both adult and child participants understood the task and performed successfully in terms of their appreciation of Paul's preferences: in the conditions where they had to judge whether Paul would like to do activities with social interactions their answers lay in the negative range whereas the answers for activities without interactions lay on the positive range. Repeated measures ANOVA with perspective (1PP, 3PP) and type of task (with SI, no SI) as within-subject factors and group (adults, children) as a between subjects factor revealed significant main effects of perspective ($F(1,22)=42.24$, $p<0.0001$) and type of task ($F(1,22)=25.88$, $p<0.0001$). There was no interaction between group and any condition (all $F(1,22)<0.144$, $p>0.707$).

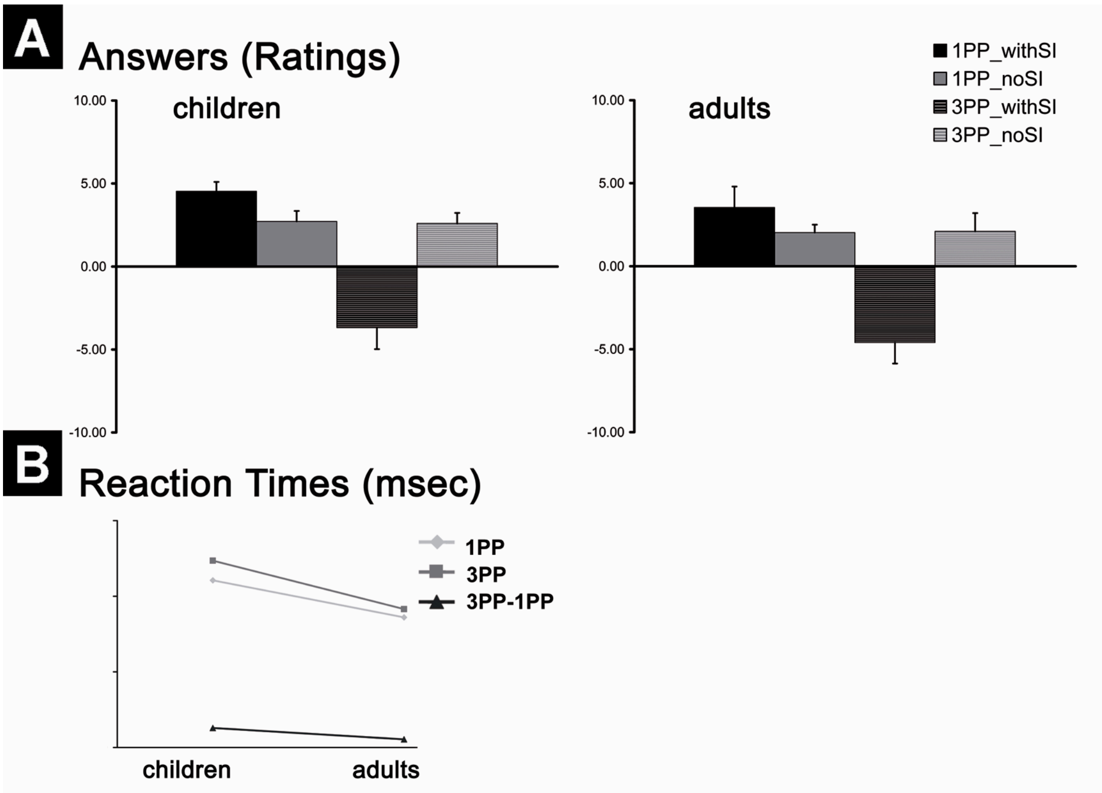

Figure 2: A) This figure shows participants' judgments (mean and standard error) according the first-person and third-person perspective (1PP, 3PP) for activities with and without social interaction (with/no SI). B) Reaction times in msec for 1PP and 3PP and reaction time differences between 3PP and 1PP judgments are shown.

Reaction times

Response times for judgments were analyzed using a repeated measures ANOVA with perspective (1PP, 3PP) and type of task (with SI, no SI) as within-subject factors and group (adults, children) as a between subjects factor. There was a main effect for perspective ($F(1,22) = 27.4$, $p<0.0001$), which indicated that judgments were made more slowly when participants had to answer according to the 3PP than when they had to answer for themselves. We further found a significant interaction between perspective and group ($F(1,22) = 5.7$, $p< 0.026$). Since there was no significant interaction between factors type of task (with SI, no SI) and perspective (1PP, 3PP) nor between the factors type of task and the group (children, adults) we collapsed trials with and without social interaction. Post hoc analysis showed that the difference between reaction times for 1PP and 3PP judgments (was significantly greater in children than in adults ($p=0.03$, mean adults: 109 msec, mean children: 292 msec) and decreased significantly with age ($r=-0.043$, $p<0.05$) (Figure 2b).

Neuroimaging Results

Main effect perspective: contrast 3PP versus 1PP judgments in children

Children showed enhanced activation in the parietal and frontal lobes during judgments for another person as compared with judgments for themselves (Table 1).

Within the parietal lobe, they activated the right and left inferior parietal cortex (BA 40), the post-central gyrus (BA 3) and the right precuneus (BA 7) and, within the frontal lobe, the right dorsolateral prefrontal (middle frontal gyrus, BA 9) and the left inferior prefrontal cortex (BA 46) and sublobar the right insula (BA 47) (Figure 3b).

Main effect perspective: contrast 3PP versus 1PP judgments in adults

In adults, the right precuneus (BA 7) and the left inferior parietal cortex (BA 40) were more activated during 3PP judgments than during 1PP judgments. No other areas showed significant activation.

Main effect perspective: contrast 1PP versus 3PP judgments

In children, the main effect of 1PP versus 3PP judgments revealed activation in the left anterior cingulate cortex (BA 32). Adults additionally activated the posterior cingulate cortex (BA 23, 24), left middle frontal gyrus (BA 8), and the left inferior parietal gyrus (BA 40).

Interactions: perspective by age-group

Voxel-based whole-brain analysis revealed no significant brain activation for the interaction between perspective and group. We therefore performed ROI analysis.

Comparisons between children and adults

For the ROI analysis we took the activation pattern from the main effect 3PP versus 1PP judgments for all participants together as described in the methods. As can be seen in Figure 3c, adults and children showed comparable brain activity in all ROIs formed from the difference between 3PP and 1PP judgments, except for the right middle frontal cortex and in the right inferior parietal cortex. Using repeated measures ANOVA with the factor perspective (1PP, 3PP) and the between-subject factor group (children, adults) the statistical analyses revealed a significant interaction between group and perspective in right dorsolateral prefrontal cortex (middle frontal gyrus) ($F(1,22)=4.27$, $p<0.05$) and the right inferior parietal cortex ($F(1,22)=4.14$, $p<0.05$), but not in the other ROIs (all $F(1,22)<0.274$ $p>0.05$). The comparison between children and adults for the ROIs from the contrast 1PP versus 3PP judgment yielded no significant main effect of group (all $F(1,22)<1.68$, $p>0.208$ group interaction with any of the ROIs (all $F(1,22)<3.515$, $p>0.074$). We further analyzed the effect of similarity between the participants and Paul by correlating the ratings of similarity with percent signal change within each ROI. None of the ROIs correlated with similarity (all $r<0.329$).

Comparison between good and bad performers

To examine whether the differences between children and adults in brain activation are predominantly caused by maturation effects or by performance differences between groups, we separated the groups into good and a bad performers (see methods). Brain activity within each ROI was analyzed using a repeated measure ANOVA with perspective (1PP, 3PP) as within-subject factor and age (adults, children) and performance (good-performer, bad-performer) as between-subject factors. Statistical analysis revealed no significant two-way and three-way interaction with performance in any brain region (all two-way interactions: $F(1,20)< 1.41$, $p>0.248$) and all three-way interactions: $F(1,20)< 3.14$, $p>0.092$).

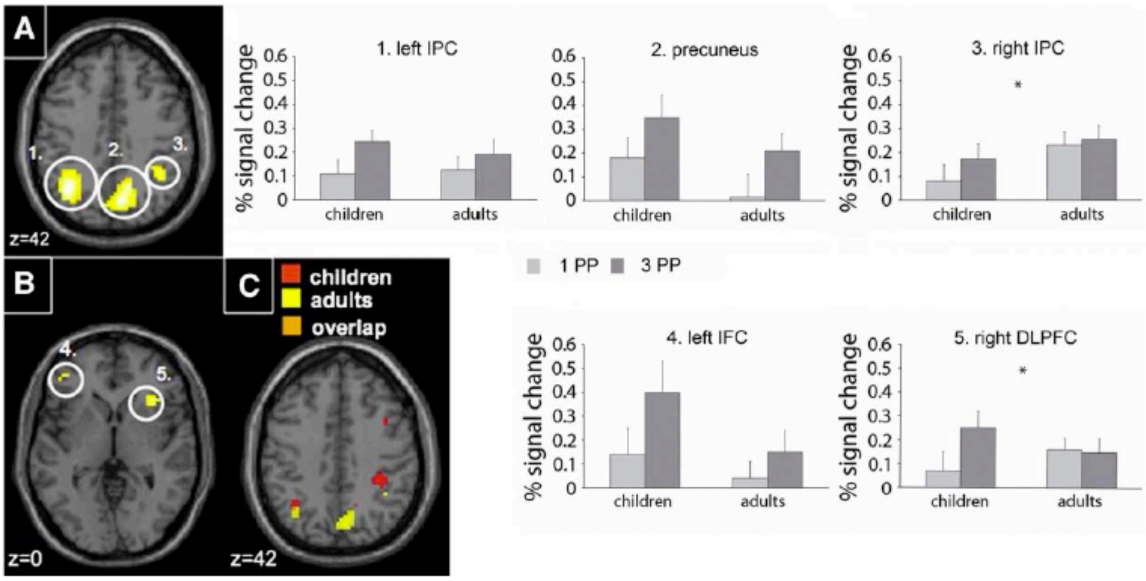

Figure 3 A-C: A-B) Theses figures show the main effect of 3PP versus 1PP judgments for all participants together. Statistical maps are thresholded at p<0.005 and overlaid on a canonical T1 anatomical image. The signal change (%) and standard error of 1PP (light grey) and 3PP (dark grey) in the ROIs of the left parietal gyrus (x=-36, y=-57, z=39)), precuneus (6, -69, 39), right parietal gyrus (39 -48 45), the left inferior frontal cortex (x=-42, y=45, z=0) and right dorsolateral prefrontal cortex (x=39, y=24, z=27). Adults and children are shown separately. Significant interactions (*) between perspective and group thresholded at p<0.05.
C) This figure shows the main effect of 3PP versus 1PP for children (yellow), adults (red) and the overlap between children and adults (orange).

Figure 4a shows the probability maps for the contrast 3PP versus 1PP. The probability-maps suggest that children deploy a more extended neural network than adults. Within the frontal cortex, the activation seems to become more focal with development and in the more posterior regions we can see a shift from bilateral to unilateral left parietal activation. For the ROIs within the frontal lobule, we could not calculate the variability in location of individual local maxima because we had to exclude 5 from 12 adults since they did not show activity within the frontal lobule for the contrast 3PP>1PP. For the ROIs in the parietal lobule, the variability in location of individual local maxima did not seem to differ between groups (Figure 4b). We had to exclude six participants from the analysis because their data did not yield activation within our predefined search range (see methods): three within the left inferior parietal cortex (2 children, 1 adult), one within the precuneus (1 adult) and two within the right inferior parietal cortex (2 adults). If at all, adults showed a larger variation than children in the right parietal cortex.

This observation was confirmed in the analysis of the mean Euclidean distance values. The distances varied in these ROIs from 9.1 to 20.5 mm (see Fig. 4c). The Mann-Whitney *U*-Test showed no significant difference in Euclidean distances between the two groups in the left inferior parietal cortex ($p>0.76$, 2-tailed) and the precuneus ($p>0.109$, 2-tailed). Within the right inferior parietal cortex we found a tendency for a group difference in the Euclidian distance ($p<0.066$), indicating that adults showed larger variability (22.5 mm) than children (14.4 mm).

Table 1: Peaks of Activity in Children and Adults during Direct Comparison of 1PP- and 3PP Processing

		MNI coordinates					
Contrast	**Area**	**BA**	**X**	**y**	**z**	**t-value**	**k**
3PP >1PP	Precuneus	31	21	-57	30	3.95	20
Children	Inferior parietal gyrus	40	36	-39	42	3.82	28
		40	-36	-57	39	3.60	19
	Post-central gyrus	3	57	-18	33	3.39	8
	Middle frontal gryrus	9	48	27	33	3.71	37
	Insula	13	33	21	0	3.33	5
Adults	precuneus	7	3	-72	48	4.24	81
	Inferior parietal gyrus	7	-33	-63	42	3.25	6
1PP > 3PP							
Children	Anterior cingulate gyrus	32	-3	45	0	4.49	20
	Brainstem		3	-39	-39	4.32	10
Adults	Anterior cingulate gyrus	32	-6	45	15	5.03	221
		24	9	27	15	4.10	9
	Cingulate gyrus	24	9	3	24	3.96	6
		32	-15	3	42	3.35	5
	Posterior cingulate gyrus	23	-12	-51	18	3.78	14
	Middle frontal gyrus	8	18	-15	63	3.74	39
	Inferior parietal gyrus	40	-57	-30	24	3.59	8

Clusters in a priori regions of interest and survive a threshold of $p<0.005$ for magnitude, $k>5$ voxels; All other clusters survive a threshold of $p<0.05$; $k>10$ voxels FWE corrected. BA=putative Brodmann's area; x, y, z =MNI coordinates; k=number of voxels in a cluster

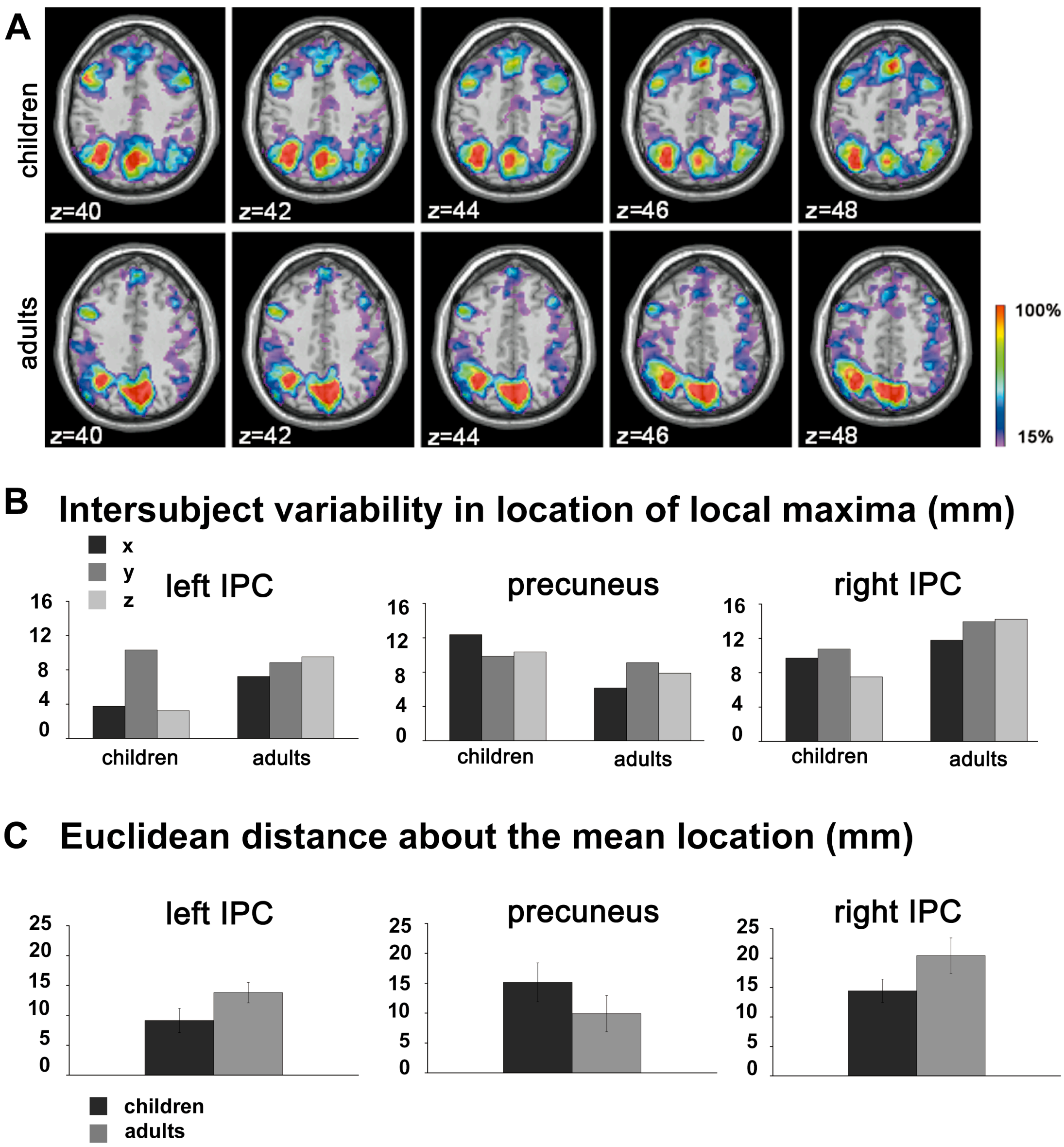

Figure. 4A-C: A) This figure shows the probability maps thresholded at p<0.05 and overlaid an a canonical T1 anatomical image for children and adults separately for the contrast 3PP-1PP.
B) This figure shows the inter-subject variability in locations of activation (mm) for each region of interest 1) left inferior parietal cortex (x= -36, y=-57, z=39; 2) precuneus (6, -69, 39); and right inferior parietal cortex (39, -48, 45). Each bar graph represents one standard deviation in x-, y-, and z-coordinates. C) Each bar graph represents the average Euclidean distance (mm) around the mean location for each brain region. The error bars represent standard errors.

5.5. Discussion

Brain activation during participants' reasoning about another person's mind was compared with brain activity when they reflected upon their own preferences Reasoning about others, and understanding what they think, what they feel or what they believe involves stepping into their 'mental shoes' and taking their perspective. The ability to understand other people's mind and realize that they can have different perspectives is commonly referred to as having a "theory of mind". It requires the ability to distinguish 'self" from 'other' and appreciate another's person intentions, beliefs or preferences.

We would argue that cognitive perspective taking becomes increasingly efficient (decrease of △RT between 3PP and 1PP) after the age at which classic theory of mind tasks are accomplishable. Additionally, development of cognitive perspective taking shows changes in brain activity within a neural network involving particularly posterior parietal regions but also prefrontal brain areas. We would further argue that increased efficiency in perspective taking during development is supported by a focalization of the neural network involved. In contrast to previous imaging studies on cognitive development we were able to show by using measures of inter-subject variability analysis that children activated a coherent but more extended neural network during judgments for others than adults.

Maturation accompanies increased efficacy in perspective taking

There is currently considerable debate about the way in which we switch viewpoints from oneself to another person in everyday social interaction. According to the simulation theory, we place ourselves in another person's position by asking what we might believe or desire in a similar situation and simulate them (Taylor et al., 1994). Alternatively, the "theory-theory" claims that that we use a common sense psychological theory to understand other people's mind, rather than internally simulating them (Gopnik and Meltzoff, 1997). However, when taking another person's perspective it is not always sufficient only to simulate what I *myself* would do in the other person's situation. I need to imagine what the other person would do in her or his situation. In addition to 'putting ourselves in another person's shoes' we therefore need to distinguish our own preferences from another person's intentions or preferences. Our behavioral data indicate that all participants, irrespective of age, inhibited their own egocentric perspective and mentally stepped outside their viewpoint to adopt the other person's preferences. Thus, in respect of this debate the ability to appreciate Paul's preferences appropriately cannot only be explained by the simulation theory. To appraise Paul's preferences appropriately participants need to develop a 'theory 'about the mind of a person like Paul.

Despite the qualitatively equivalent performance between children and adults, we quantitatively found a significant interaction in reaction times between group and perspective, which indicated that differences between self and other judgments decrease with age. The reaction time differences could not have been due to any differences in stimuli since we presented the same stimuli in both conditions. Several studies in adults have reported longer reaction times for 3PP than for 1PP (D'argembeau et al., 2007; David et al., 2006; Vogeley et al., 2004), although in some studies the differences were not significant (Ruby, 2003, 2004). In this context Choudhury and colleagues recently compared 3PP and 1PP reaction time differences between children, adolescents and adults (Choudhury et al., 2006). They also found a significant decrease in reaction time differences with age but in contrast to our findings the difference between 3PP and 1PP spread almost equally in both directions (3PP>1PP and 1PP>3PP), whereas none of our children showed faster reaction time for 3PP than for 1PP. Taken together, our behavioral results indicate that perspective taking in children seems to be generally established, but that their way of processing is less proficient than in adults.

Neural development of perspective taking

The focus of the present study was the development of the neural bases for processing other person's mental perspectives. The present data for 1PP processing are in good accordance with studies on neural correlates related to the self-processing and with self- perspective studies (Damasio et al., 2000; Piefke et al., 2003; Vogeley et al., 2004). Since we did not find any developmental differences in brain activity related to 1PP processing, subsequently only brain activation that is associated with 3PP processing will be discussed.

For 3PP compared to 1PP processing, adults activated the precuneus and the left inferior parietal cortex. Children additionally activated the left inferior frontal cortex, the right dorsolateral prefrontal cortex and the right parietal cortex. The significant interaction between age and perspective n the right dorsolateral prefrontal and in the right inferior parietal cortex indicates that these cortical regions play an important role in the development of perspective taking.

An increasing number of imaging (Ruby & Decety, 2001, 2003, 2004; Saxe, 2006; Saxe et al., 2005) and lesion studies in adults (Samson et al., 2004) point to the importance of the posterior parietal regions in relation to perspective taking. It has been proposed that the inferior parietal cortex is critical for the ability to distinguish between self and other (Decety et al., 2003b). This region was specifically involved when participants imagined another person being the agent of an action, imagined how another person feels in a given situation, what another person thinks or how another person experiences pain but not when they imagined these situations for themselves (Jackson et al., 2006; Ruby & Decety, 2001, 2003, 2004). Several studies in adults reported that the inferior parietal cortex in the right hemisphere was mainly involved in perspective taking whereas others found it more in the left hemisphere (David et al., 2006; Vogeley et al., 2004). Even clinical neuropsychology reported mixed findings. Samson and colleagues (Samson, 2004) reported evidence from three brain-damaged patients that the left TPJ is necessary for reasoning about other person's mind, while Blanke and colleagues (Blanke, 2002) referred to the importance of the right hemisphere. In the latter study direct cortical stimulation of this region induced an out-of-body experience, which is a 3PP of oneself. So far the contribution of each parietal lobule is still unclear since lateralization effects have not been investigated systematically. However, two recent studies demonstrated a selective impairment of self-other distinctions when repetitive transcranial magnetic stimulation (TMS) was applied over the right inferior parietal lobule as participants performed a perceptual task involving discrimination between photographs of themselves and of a familiar face (Uddin et al., 2006). Self-other judgments on whole arm reaching movements (Preston et al., 2008) were also impaired when TMS was applied over the right but not over the left inferior parietal cortex. The additional 3PP specific activation in the right IPL in children compared with adults might therefore indicate that children need more self-other discrimination during 3PP processing than adults.

In comparison to adults, children additionally activated prefrontal brain regions during the processing of another person's perspective. The significant interaction between age and activation in the right dorsolateral prefrontal cortex indicated that only children specifically activated the right dorsolateral prefrontal cortex during 3PP.

Even though there are only a few studies on the development of the neural network underlying social cognitive processes, several authors reported a decrease of frontal activation with age. Using a similar task, Pfeiffer et al. (Pfeifer et al., 2007) found the medial prefrontal cortex (mPFC) more activated in children than in adults while they reported whether short phrases described themselves or a highly familiar other person (Harry Potter). Another neuroimaging study found that the mPFC was more active in adolescents than in adults while participants were thinking about their own intention compared to thinking about physical causality (Blakemore et al., 2007). Because both of these studies focused on self-related processing comparison with our results is limited. Wang and colleagues investigated the development of the ability to understand irony, which requires the ability to separate the literal meaning of a comment from its intended meaning. Again, children and adolescents activated the mPFC and the left inferior frontal gyrus more than adults (Wang et al., 2006, 2007).

Thus, the present findings seem to be in line with the previous developmental studies in terms of the decrease of prefrontal brain activation. However, in contrast to the reported findings we mainly observed a decrease in activation within dorsolateral prefrontal cortex (DLPFC) instead of medial prefrontal cortex. The DLPFC is known to play a critical role in executive function, particularly in cognitive control (Aron et al., 2004; Blasi et al., 2006; Bunge et al., 2002; Fecteau et al., 2007; Knoch et al., 2007; Knoch et al., 2006; Menon et al., 2001). From developmental psychology we know that higher cognitive control and attention functions develop long into adolescence (Davidson et al. 2006). Interestingly several social psychological studies have demonstrated that even adults frequently use self-knowledge as the primary basis for developing a model of what others know and feel, which has been described as a default mode of reasoning about others' mind. This egocentric bias can be interpreted as failure to suppress one's own perspective (Gilovich et al., 2002; Nickerson, 1999; Royzman et al., 2003; Vorauer et al., 1999). Considering this background the 3PP specific activation of the DLPFC in children may indicate that processing a 3PP requires children more than adults to inhibit their own prepotent egocentric perspective while they reason about Paul's perspective.

A possible explanation for the differences in brain activation in children compared to adults is cortical maturation, in particular grey matter reorganization and white matter increase throughout adolescence and early adulthood. Since the prefrontal cortex and the inferior parietal cortex are among the last brain regions to mature (Gogtay et al., 2004) it is plausible that these region contains less well functioning connections, leading to more activation for tasks that recruit them. Alternatively one can argue that more attention is needed by children to perform the task (judge according to Paul). Since we did not find performance related differences in brain activation we can rule out this argument.

In addition to the frontal and parietal cortex we found the precuneus to be specifically involved in 3PP processing in children and even more pronouncedly in adults. Several perspective taking studies found that the precuneus was activated during perspective taking. Its posterior part, which we found to be involved in 3PP processing, has recently been found to be preferentially activated during recollection of imagined rather than viewed items (Lundstrom et al., 2005). Since participants did not personally know Paul and due to the fact that the story about him did not contain any explicit hint about how to answer the questions, they really had to imagine Paul's preferences rather than retrieve information from memory. The precuneus is also known as part of the so called "default network": A network of brain structures (including medial frontal, parietal and temporal areas) displaying the highest metabolic rates when participants are at rest but are 'deactivated' during cognitively effortful tasks (Gusnard et al., 2001; Raichle et al., 2001). However, in the context of our results its worth mentioning that there is a remarkable overlap between brain areas typically involved in social cognitive tasks and the 'default system'. Thus, it has been argued that the resemblance of brain regions engaged in social cognition as well as during "resting states" suggest that human beings might have a predisposition for social cognition to which they return when not explicitly forced to an effortful task (Schilbach et al., 2008). At this point we refer to Cavanna (2006) for review about the precuneus and its functional and behavioral correlates (Cavanna et al., 2006) and at Schilbach (2008) for an excellent overview about the relation between the default and the social cognitive networks of the brain.

Intersubject variablity in location of brain activity

Previous neuroimaging studies on development, reported similar patterns of neural activation among children and adults, whilst children convey more distributed patterns of neural activation and a decrease of BOLD signal as compared to adults. Such a change in patterns of neural activity has been referred to as a focalization of neural development (Casey et al., 2005;

Durston et al., 2006). The usual explanation for greater variation in neural activity across brain regions is that cognitive strategies are less efficient in children, whereas enhanced activity in focal brain areas during maturation has been interpreted as being due to increased efficiency and neural pruning. A problem, however, with interpreting focalization in brain imaging is that differences in neural activity can be confounded by differences in variability between groups: a more heterogeneous or incoherent pattern of neural activity not only leads to a more distributed network but also to a reduction of neural activity. Thus, to determine if focalization of neural activity during maturation occurs, one has to disentangle measures of variance and measures of signal change (Berl et al., 2006; Xiong et al., 2000).

The probability-maps (figure 3a) showed that children deploy a more extended neural network than adults. Probability maps provide support for a developmental shift from frontal to posterior and from bilateral to unilateral within parietal activation. Since 5 adults did not show any frontal brain activation for the contrast 3PP>1PP, the comparison of the inter-subject variability in location of frontal brain activity between children and adults could not be calculated (figure 3b-c). In parietal areas, we found no indication for lower activation in children, while the probability maps indicate that children activate a more extended network than adults. Additionally, children showed a similar (or even reduced) degree of variance in the distribution of local maxima in neural activity as compared with adults. These findings suggest that children activated a coherent but more extended neural network of activity. This pattern of neural development is compatible with the hypothesis that an immature network has extensive activation because the network is not fully pruned. The findings do not support hypotheses on diffuse and dispersive networks in children, as has been suggested for different tasks (Berl, 2006, Durston, 2006).

Three potential weaknesses of the study should be mentioned: first, the significance of the study may be hampered due to the small sample sizes of the two groups. Second, the ability of taking another person’s perspective may depend on the similarity or dissimilarity, respectively, of that person to the own personality, which might have an impact on brain activation. We obtained the degree of similarity only by asking participants how much they feel alike Paul generally and did not find any significant correlations. For further studies, it would be interesting to explore the degree of similarity in more detail (for example by using a questionnaire) and investigate how it influences the ability to reason according to a third-person's perspective in children and adults and furthermore to explore its effect on brain activation. In this context Mitchell (Mitchell et al., 2006) could show that a region in the mPFC linked to self-referential thoughts was activated during judgments according the perspective of a similar other person but not according a dissimilar other person. The overlap between judgments of self and a similar other person suggest that participants can use knowledge about themselves to infer the mental states of similar others. Moreover, since children show more difficulties in cognitive control, it would be interesting to explore the degree of self-suppression during perspective taking in dependence of the similarity to the other person. Third, according to Kriegeskorte (Kriegeskorte et al., 2009) there is a certain danger to commit a type I error by using the same dataset for statistical analysis and generating ROIs. Since we only built ROIs 1) after verifying our hypotheses about the brain location associated with processing a third-person's perspective (prefrontal cortex and inferior parietal cortex) and 2) for each significant cluster (there was no selection of clusters) we argue for the present approach. There would have been the possibility to built ROIs according to the literature to test our hypothesis. Since we were especially interested in developmental effects and there is no developmental study investigating perspective taking in children or adolescents, we would have missed important information by generating ROIs according to the adult literature. We nevertheless additionally performed a ROI analysis according to the literature. An adult study for our hypothesis about the parietal cortex brain activation and a developmental study for the hypothesis about the prefrontal cortex activation were used. The results confirmed our findings about the decrease of prefrontal cortex activation with age. In contrast to our ROI analysis in the right inferior parietal cortex there was no significant interaction between perspective and age-groups in the ROI of the right inferior parietal cortex based on the literature (see supplementary materials).

We conclude that the neuronal network underlying perspective taking is generally established in eight year old children: 1) because children showed no more variance within the adult neural network, 2) because the more widespread activation patterns cannot be explained by greater inter-subject variance in children, 3) because the variability between areas within the children's network did not differ, and 4) differences in neural activity can be attributed to maturation, not to performance differences between adults and children. Children use a coherent but larger neural network to solve the task. One might speculate that children have not yet developed a specific approach to infer the perspective of others and thereby activated additional regions. Since adults are more experienced in social interaction with a variety of different personalities and thus are more skilled in perspective taking, they may have developed specific "modules" and use an efficient strategy to think about Paul's preferences, which presumably has been learned and reinforced from past experiences.

Taken together this is the first study on cognitive perspective taking in children that reveals the development of neural networks beyond the age of eight years. From developmental psychology studies we know that higher order cognitive function such as cognitive control develops into adolescence and is relevant in relation to a number of developmental disorders. The development of perspective taking abilities beyond six years of age is much less investigated, although respectful and considerate behavior cannot emerge without a sophisticated understanding of other people's perspectives.

The developmental differences we observed in this study cannot be attributed to qualitative performance differences since the behavioral output is the same in both age groups, but it seems that the children's strategy is less efficient (longer reaction times). Furthermore, we have been able to specify that neural development of perspective taking accompanies a shift of brain activity from frontal to posterior brain regions and from bilateral to unilateral left brain activation in the parietal lobule. This supports and extends the focalization model of neural development. Since the additionally activated right inferior parietal cortex in children did not show more inter-subject variability than the other brain areas, we conclude that children use a qualitatively different, but coherent network.

6 Adopting another person's mind: girls and boys neural development of cognitive perspective taking[2]

Dosch M, Loenneker T, Klaver P*, Martin E*

* authors equally contributed

6.1. Abstract

Adolescence is characterized by a transitional period of physical and psychological changes. The neural basis of these developmental changes is controversially discussed, particularly in the light of male and female development. Here, we investigated the neural development of perspective taking in children, young adolescents and adults of both genders by comparing brain activity during judgments from a third-person's perspective (3PP) with judgments from the first-person perspective (1PP). Behaviorally, children, adolescents and adults did not differ in appreciating a 3PP but the reaction times for 3PP versus 1PP judgments differed between pubescent girls and boys. Functional brain imaging results revealed pronounced activation of a fronto-parietal network during 3PP as opposed to 1PP judgments. Furthermore, we observed developmental gender-differences within this network. Whereas in females the development of the functional network was characterized by a decrease in activity in the right dorsolateral prefrontal cortex, changes in laterality within the inferior parietal cortex were observed in males. These results warrant the conclusion that neural development of social cognition differs between males and females, which is particularly striking during adolescence.

[2] Article submitted to Journal of Social Cognitive and Affective Neuroscience

6.2. Introduction

Humans are social beings. The human ability of mutual understanding and to predict the actions of others is essential for successful social interaction. A central mechanism of social understanding is the ability to step into other peoples 'mental shoes' and reason according to their perspective to understand what they think, feel or belief. In the present study we investigate the ability to take other person's mental perspective.

A number of functional neuroimaging studies in adults have investigated the neural mechanisms underlying the ability to represent the mental state of other people. They often compared neural responses while imagining another person's perspective (a third-person perspective; 3PP) with those during the imagination of their own perspective (first-person perspective, 1PP). Third-person's perspective compared to one's own perspective has been associated with brain activation in the inferior parietal cortex, the medial posterior cortex, i.e. the posterior cingulated and the precuneus, and the prefrontal cortex (David et al., 2006; Jackson, Meltzoff et al., 2006; Lamm et al., 2007; Ruby et al., 2001a, 2003, 2004; Vogeley et al., 2001).

Recent structural MRI studies have demonstrated that the brain undergoes considerable developmental changes during adolescence. While the global grey matter (GM) volume of the cerebrum decreases (Giedd et al., 1999), the white matter (WM) volume increases (Giedd et al., 1999; Paus, 2005). Moreover, a region-specific developmental decrease in GM volume has been reported in frontal, parietal and temporal areas (Giedd et al., 1999; Gogtay et al., 2004; Sowell et al., 2004; Sowell et al., 2002; Wilke et al., 2007), which differs between boys and girls. Theses changes in frontal and parietal cortices occur one to two years earlier in boys than boys. In this context it has recently been suggested that the development of the adolescent brain might respond differently to changing levels of testosterone and estradiol. E.g. it could be demonstrated that the levels of sex steroids in children between 8 and 15 years of age were associated with sexual dimorphic gray matter areas (Neufang et al., 2009). The reported neuroanatomical changes during adolescence may reflect a refinement of neuronal connections that could be related to cognitive and emotional development. It can be further hypothesized that functions that relay on these brain regions would also show developmental changes during this time period.

Given the fact that brain imaging studies on perspective taking in adults have identified the importance of a fronto-parietal network and that structural studies have demonstrated developmental changes of these regions to continue until early adulthood and to differ between girls and boys, we hypothesize developmental differences in the neural network underlying cognitive perspective taking between genders.

To test this hypothesis we scanned 12 children, 11 young adolescents and 12 adults of both sexes. They were required to make judgments on leisure activities for themselves (1PP) or for another person (3PP). Leisure activities are much more self-defining during adolescence than school activities because they provide more opportunity for self-direction and initiative. During the task short statements of real life situations were presented to both adults and children, who were required to make judgments for themselves and for another person.

Since brain imaging studies on perspective taking in adults pointed the importance of the fronto-parietal network and structural studies showed that this network is not fully developed until early adulthood we expected that the neural development of perspective taking is associated with changes in brain activation within the prefrontal cortex and the inferior parietal cortex. Moreover, given that structural studies reported differential neural development across males and females we were especially interested in gender-specific developmental differences.

6.3. Methods

Participants

Data were acquired from 12 children (aged 8.5-10.6 years, *mean* 9.9, 6 females), 11 young adolescents (aged 11.8-13.1 years, *mean* 12.6, 5 females) and 12 adults (aged 24.6-32.3 years, *M*=29.1, 8 females). Four additional children and two male adults had to be excluded due to extensive movement during the fMRI scanning (>5mm) and were therefore also excluded from behavioral analysis. All children were recruited from public schools in the city of Zurich. Participants completed the German version of the autism-spectrum quotient questionnaire for adults or for children (AQ, Baron-Cohen, 2006) – a quantitative self-report instrument for assessing how many autistic traits a person has. None of the participants scored above the critical minimum of 30 out of 50 autistic traits (children: m=18.73, sd=5.10; adolescents: m=14.3, sd= 6.65; adults m=16.35, sd=4.56). No significant group differences ($t(2,32)$=,1.74, p=0.192) or sex differences were found ($t(1,32)$=0.054, p=0.818). Participants were also asked to indicate on an analogous scale (ranging from 0-100) how much they felt like Paul irrespective of sex. Female and males did not differ in their ratings (males: m=17.00, sd=19.80; females: m=15.06, sd=12.636 F(1,33)=1.22, p=0.73) but there was a significant group difference (children: m=29.92, sd= 18.50; adolescents: m=3.10, sd=2.28; adults: m=13.75, sd=8.27), F(1,33)=14.76, p<0.0001). All participants were right-handed as assessed by the Edinburgh Inventory Scale (Oldfield, 1971). None of the participants had a significant history of medical, psychiatric or neurological disorders on the basis of self- or parent-report. None of the participants used any neurotropic or psychotropic medication. Written informed consent was obtained from all participants, as well as written informed parental consent for child participants. The study was approved by the local ethics committee and conducted in accordance with the guidelines set out in the Helsinki Declaration

Task Description

Children and adolescents were introduced to the “other child” by reading a story about Paul a child with autistic behavior; adults likewise learned about a grown-up person with autistic behavior. During the fMRI measurement, the task required participants to make judgments about 32 leisure activities for themselves or for Paul. Activities with and without social interactions (with SI, no SI) were chosen to provoke differences in judgment for the 1PP and 3PP condition (assuming that Paul would dislike all social interactions). Separate task versions were created for children and for adults. The task employed a design in which the type of stimulus and the perspective taken by the participants was manipulated. In the 1PP condition, subjects were asked to evaluate how much they like to do certain activities. In 3PP condition, subjects were instructed to imagine Paul and answer according to his preferences and interests and to ignore their own. In all trials, subjects were presented first with a picture if themselves or of Paul (duration 2 seconds) to indicate the perspective they had to adopt for answering the upcoming question. Subsequently, a sentence (e.g. ‘going to a friend’s birthday party’ or ‘reading a book’) was presented in black on a grey background (duration 6 seconds) together with a slider for answering, followed by a fixation cross (500 ms). Sixteen null-events in which only a fixation cross was shown were included and presented randomly. Participants were required to make their judgment by pressing the left or right button with the middle or index finger of their right hand. The button press moved a red marker on a slide on a continuous scale from left “I don’t like to do this activity at all” to right “I like to do this activity very much” (the scale range was from -100 to +100 with no visible scale in between). The longer the left/right button is pressed, the more the slider moves to the left/right side of the scale. The starting point of the red marker on the continuous scale was presented randomly. Each of the four conditions (1PP with SI, 1PP no SI, 3PP with SI, 3PP no SI) consisted of 16 trials which had to be judged according to both perspectives (total 64 trials). The sequence of the trials was generated randomly for each participant. Each activity had to be judged for them selves as well as for Paul.

Experimental Procedure

Before the scanning session we introduced the participants to “the other person”, Paul. Then, they were instructed to learn about the other person by reading a story about the history of a male child, or adult with autistic behavior describing his social behavior and academic skills as well as his interests. Participants did not know that Paul has the diagnosis of Asperger Syndrom. We used different versions for adults and children. The difference between histories was that Paul’s biography continued until adulthood for adults, but stopped at childhood (ca. 10 years) for the children. Similarly, the photograph of Paul was adapted to the age of the participants. The story comprised 200 words for children and 293 for adults. Participants were then asked to retell the story and answer several questions to ensure that they understood correctly and could imagine the Paul’s personality. After introducing participant to Paul we carefully instructed them in the whole fMRI procedure and explained the task. Participants then practiced 5 trials from the 1PP and 5 from the 3PP. We again emphasized that it was very important to really try to imagine Paul and that we were interested in seeing how their brain works while they are thinking of him. We used MR-compatible video goggles to present the stimuli and additional acoustic noise protection by headphone (MRI Audio/Video System, Resonance Technology, Inc., USA) throughout the examinations. The task was programmed by Cogent implemented under MATLAB (http://www.vislab.ucl.ac.uk/CogentGraphics/)

MRI Data acquisition and analysis

BOLD sensitive images were collected on a 3.0 Tesla General Electric MR-scanner using a gradient-echo EPI-sequence with a repetition time of 2000 ms and a 64x64 matrix. Altogether, 32 slices were aligned to the anterior and posterior commissure (flip angle = 50º, FOV= 24cm, slice thickness per volume = 3.8mm, 360 repetitions). Secondly, a three-dimensional T1-weighted anatomical scan (FOV = 230 mm x 198 mm x 158 mm, matrix = 224x192x132; TR = 8.6 ms; TE = 2.1 ms) of the whole brain was acquired. Images were analyzed using SPM5 (Statistical Parametric Mapping software, Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm). The fMRI data were realigned for movement correction, normalized to the SPM template with a resampled voxel size of 3 mm^3 and smoothed with a Gaussian kernel (full width at half maximum: 9mm).

For each participant the expected hemodynamic responses at the onset of the four conditions were modeled by two response functions, which were a canonical hemodynamic response function (HRF) and its temporal derivative (Friston et al., 1998).

The functions were convolved with the event train of stimulus onset to create covariates in a general linear model. Misses were modeled as a parameter of no interest. Parameter estimates for four conditions (1PP with SI, 1PP no SI, 3PP with SI, 3PP no SI) were obtained by maximum-likelihood estimation while using a temporal high-pass filter (cut-off 128 s) and modeling temporal autocorrelation as an AR(1) process. Since the neural development of perspective taking was the focus of our interest, we collapsed trials with and without social interaction.

In a voxel based analysis comparison between each condition and rest, and direct comparison between conditions were thresholded at $p<0.05$ (FWE corrected, $k>10$) and $p<0.005$ (uncorrected, $k>5$ voxels) for regions for which we had a strong a priori hypothesis, namely, the prefrontal and parietal cortex (Forman, 1995, Pfeiffer, 2007).

To specifically look at developmental and gender-related effects of perspective taking we calculated a ROI analysis on basis of the activation pattern form the main effect of 3PP and 1PP judgments. Because we have three independent groups the ROIs were based on the activation patterns across all participants (3PP>1PP), FDR corrected with a threshold of $p=0.05$).

According to these main effects 10mm spheres around each local maxima of each significant cluster for the contrast 3PP>1PP were created using marsbar (http://marsbar.sourceforge.net/). We did not construct any ROI from the contrast 1PP versus 3PP since the focus of our interest was the development of processing other people's perspectives. Mean percent signal changes were taken from the raw data of every study participant for all conditions and activated voxel. The following coordinates: the right middle frontal gyrus (x = 45, y = 27, z = 36), the right posterior cingulate gyrus (x=9, y=-21, z=27), the right inferior parietal cortex (x=42, y=-51, z=45), the left inferior parietal cortex (x = -33, y = -60, z = 42), and the right precuneus (x = 6, y = -69, z = 42). For statistical analysis we used a repeated measure ANOVA with the within-subjects factor perspective (1PP, 3PP) and the between-subject factors group (children, adolescents, adults) and gender (male, female) for each ROI.

6.4. Results

Behavioral Data

Judgments

By choosing activities with and without social interaction we evoked differences in judgment for self and other conditions. The results show that all participants understood the task and performed successfully in terms of their appreciation of Paul's preferences. In the conditions, where they had to judge whether Paul would like to do activities with social interactions their answers lay in the negative range, whereas the answers for activities without social interactions lay in the positive range. Repeated measures ANOVA with perspective (1PP, 3PP) and type of task (with SI, no SI) as within-subject factors and group (adult, adolescents, children) and gender as between subject factors revealed significant main effects of perspective ($F(1,34)=64.5$, $p<0.0001$) and type of task ($F(1,34)=47.0$, $p<0.0001$). The interaction between perspective and type of task (with SI, no SI) was also significant ($F(2,33)=38.0$,

$p<0.0001$). There was no significant interaction with gender and any condition nor between age-groups and any condition all $F(2,33)>1.161$, $p>0.290$ (Figure 5a).

Response times

Response times for judgments were analyzed using a repeated measure ANOVA with the factors perspective (1PP, 3PP), and gender and age-group (children, adolescents, adults) as between subject factors. There was a main effect for perspective ($F(2,33) = 31.2$, $p<0.0001$), which indicated that judgments were made more slowly when participants had to answer according to 3PP than when they had to answer for themselves. A main effect of group, ($F(2,33)=9.7$, $p=0.001$) demonstrates that the three groups differ in response time irrespective of perspectives (Figure 6b). We further found a significant interaction between perspective and age-groups ($F(2,33)=6.6$, $p=0.004$) indicating that adolescents show less difference in RT between the 3PP and the 1PP condition (△RT) compared to children and adults. The additional significant threefold interaction between perspective, group and gender ($F(2,33) = 3.3$, $p=0.05$) shows that this effect is mainly explained by female adolescents, since they were equally fast for self and other (Figure 5b).

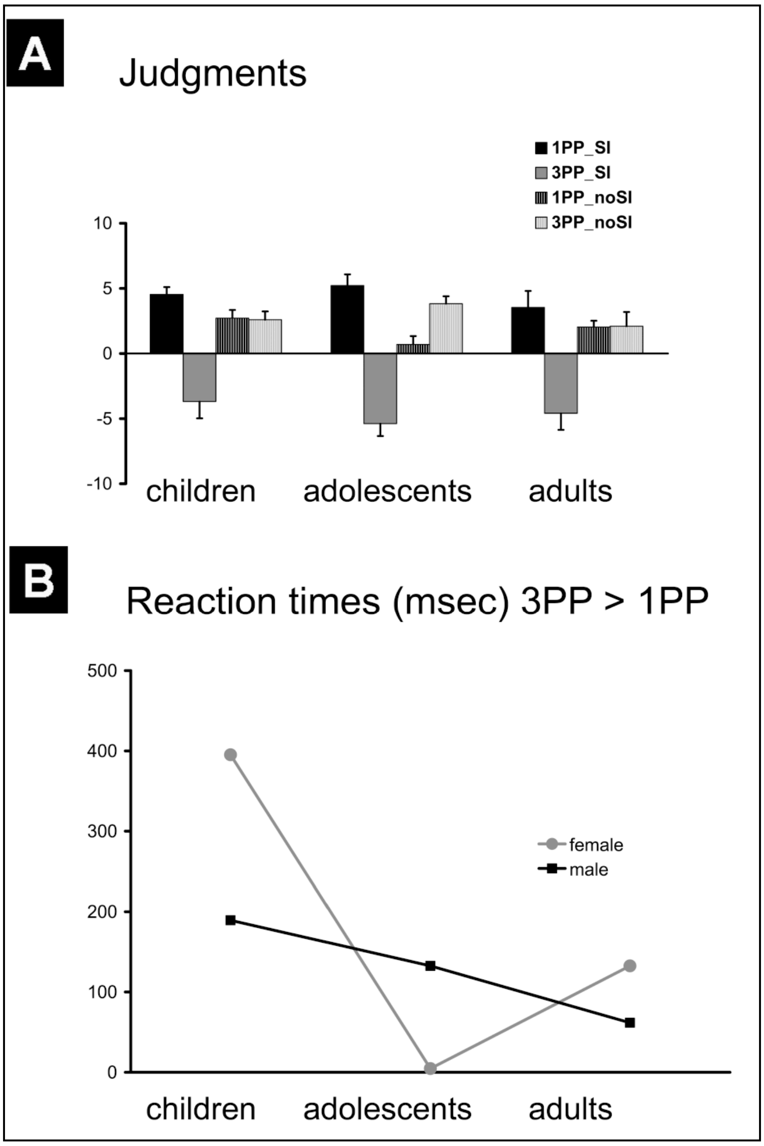

Figure 5A-B: A) This figure shows participants' judgments (mean and standard error) according to the first-person- and third-person perspective (1PP, 3PP) for activities with and without social interaction (with/no SI). B) Reaction times differences in msec. between 3PP and 1PP judgments are shown for female and male children, adolescents and adults.

.

Neuroimaging Results

Common brain activation in children, adolescents and adults of both sexes

When 3PP-judgments were compared with 1PP-judgments across all participants increased BOLD signal changes were found in the left and right inferior parietal lobule, the right precuneus, the right cingulate gyrus and the middle frontal gyrus (dorsolateral prefrontal cortex, DLPFC), the medial frontal gyrus and the right insula.

The contrast 1PP versus 3PP revealed activation in the left posterior and anterior cingulate gyrus, the left medial and superior frontal gyrus, the right fusiform gyrus, left parahippocampal gyrus and in the basal ganglia, namely the left caudate body, the left pons (Table 2).

Development of the network underlying perspective taking

For the ROI analysis we took the activation pattern form the main effect 3PP versus 1PP judgments for all participants together as described in the methods. Using repeated measure ANOVA with perspective (1PP, 3PP) and ROI as within-subject factors and gender and age-groups as between-subject factors (for details see methods) the statistical analysis revealed a significant interactions between ROI and age-groups ($F(2,33)=3.8$, $p=0.034$), a threefold interaction between ROI, perspective and gender ($F(1,34)=7.6$, $p=0.010$) and a trend towards a threefold interaction between ROI, perspective and age-groups ($F(2,34)=2.6$, $p=0.091$). Therefore we did further post hoc analysis on each ROI with a significant main effect of perspective separately.

In the middle frontal cortex, there was a significant interaction between perspective and age-group ($F(2,33)=3.24$, $p=0.05$) and an almost significant threefold interaction between perspective, age-group and gender ($F(2,33)=3.1$, $p=0.06$). The separate analysis of male and female participants showed that the effect of perspective in males was absent in all three age-groups. In females we found a main effect of perspective (more percent signal change for 3PP than for

1PP condition) and significant interaction between perspective and group, which indicated that the involvement of the dorsolateral prefrontal cortex (DLPFC) during perspective taking (Figure 6b) decreases with age and was absent in adult females.

In the left inferior parietal cortex there was, in addition to the main effect of perspective ($F(1,34)=5.7$, $p=0.023$), a significant main effect of gender ($F(1,34)=6.7$, $p=0.015$) which indicated that females showed significantly more activity than males in this area irrespective of age and perspective.

We did not find a significant main effect for perspective within the right inferior parietal cortex, but the interaction between perspective and gender was significant ($F(1,34)=4.8$, $p=0.04$). Whereas males irrespective of their age did not activate this region during perspective taking (no significant main effect), females activated this region more for 3PP than for 1PP (significant main effect of perspective ($F(1,24)=5.7$, $p=0.04$), which was especially pronounced in female adolescents (Figure 6).

Table 2: Peaks of activity in all participants during direct comparison of 1PP- and 3PP processing

Contrast	Area	MNI coordinates					
		BA	x	y	z	t-value	k
3PP>1PP	Left Inferior Parietal Lobule	40	-33	-57	42	5.43	248
	Right Precuneus	7	6	-72	36	5.43	144
	Right Inferior Parietal Lobule	40	42	-48	42	4.57	42
	Posterior Cingulate Gyrus	23	9	-21	27	4.20	6
	Right Middle Frontal Gyrus	9	45	27	36	4.04	8
	Right Insula*	13	33	21	0	4.25	52
	Right Cingulate Gyrus*	23	9	-21	27	4.11	33
	Right Medial Frontal Gyrus*	6	6	39	42	3.34	23
1PP>3PP	Left Posterior Cingulate Gyrus	23	-9	-54	18	5.83	167
	Left Medial Frontal Gyrus	10	-9	48	9	5.29	48
	Left Pons		0	-39	-39	5.05	21
	Left Superior Frontal Gyrus	9	-21	36	36	4.33	26
	Left Cerebellum		-12	-39	-9	4.23	8
	Left Caudate Body		-15	21	15	4.21	3
	Left Parahippocampal Gyrus	35	-27	-18	-24	4.18	17
	Left Anterior Cingulate Gyrus*	32	-6	45	6	5.23	370
	Right Fusiform Gyrus*	30	36	-12	-30	3.69	22
	Left Cingulate Gyrus*	31	-21	-24	36	3.59	45

Table 2
$p<0.05$, FDR corrected, MNI coordinates (x, y, z). BA= Brodmann's area if applicable. k= number of voxels in a cluster. *uncorrected, $p>0.005$, $k>10$

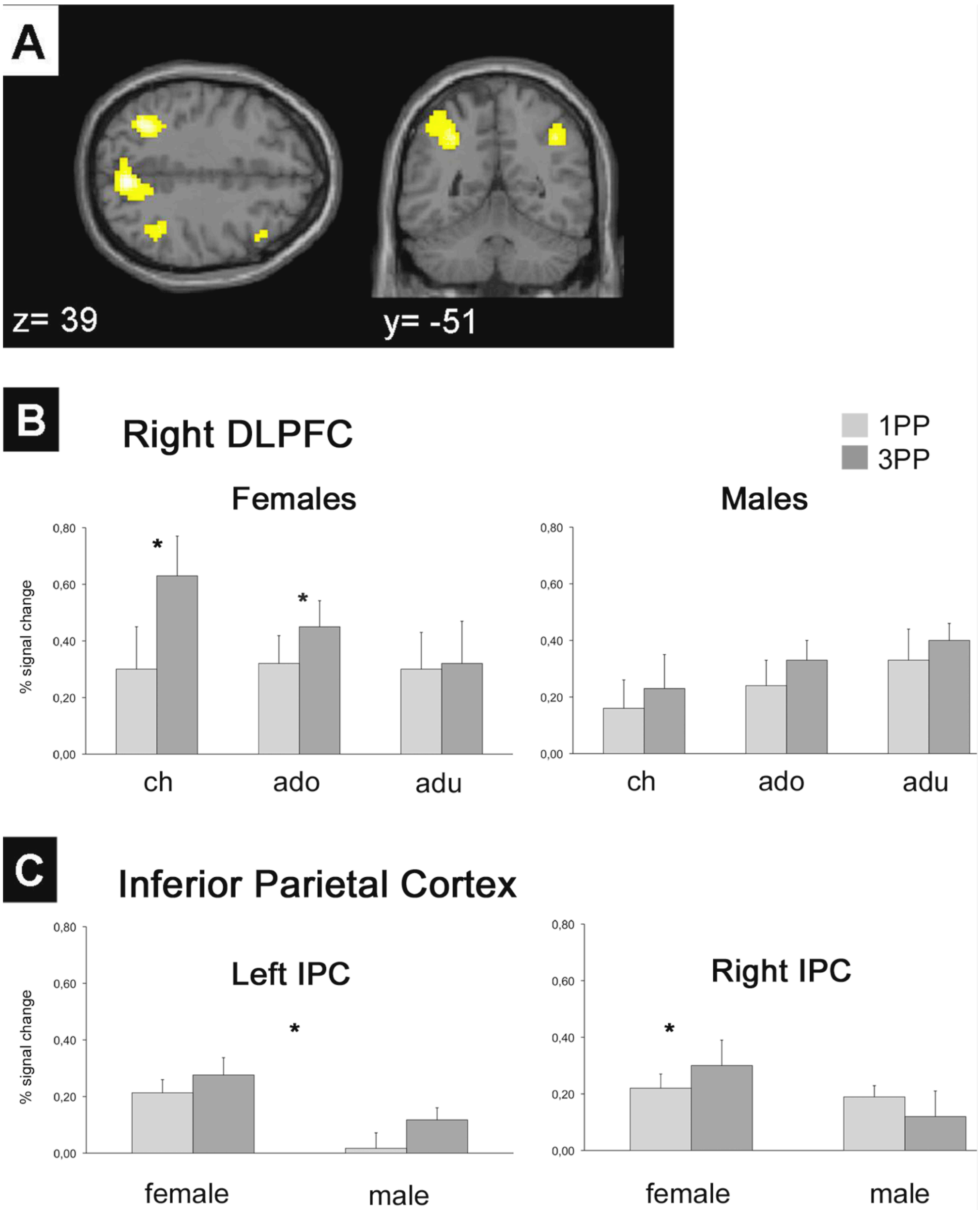

Figure: 6 A-C: A) This figure shows the main effect of 3PP versus 1PP judgments for all participants together. Statistical maps are thresholded at $p<0.05$, FDR corrected and overlaid on a canonical T1 anatomical image. B) This figure shows the signal change (%) and standard error of 1PP (light grey) and 3PP (dark grey) in the ROIs of right dorsolateral prefrontal cortex (x=45, y=27, z=36) for female and male children, adolescents and adults separately. Significant main effects (*) for perspective are thresholded at $p<0.05$. C) This figure shows the signal change (%) and standard error of 1PP (light grey) and 3PP (dark grey) in the ROIs of left parietal cortex (x=-33, y=-60, z=42) and the right inferior parietal cortex (x=42, y=-51, z=45) for female and male. Significant main effects (*) for perspective and significant interaction between perspective and gender are thresholded at $p<0.05$.

Percent signal change in relation to reaction times in female and male children and adolescents.

Since perspective taking becomes increasingly efficient with development in males and females (decreasing △RT), we analyzed how efficiency (measured by reaction time differences between 3PP and 1PP) is related to the development of the neural network underlying perspective taking in males and females. Using regression analysis between △RT and percent signal change between 3PP and 1PP (△%signal change) for each ROI, we found a significant regression between △RT and △%signal change in the DLPFC in females, which indicates that the longer participants had to consider 3PP in relation to 1PP the more they activated the frontal cortex, $F(1,18)=8.55$, $p=0.009$. In males the regression was not significant (Figure 7a). Since we found more bilateral inferior parietal activation in females than in males we calculated a laterality index of parietal activation and analyzed how the degree of lateralization is related to reaction times. The regression between △RT and lateralization (△%signal change for left and right inferior parietal cortex) in males was significant, $F(1,15)=6.02$, $p=0.028$ and indicated that the longer the RT for 3PP judgments compared with 1PP judgments were the more their parietal activation was lateralized to the left hemisphere. Females yielded no significant regression (Figure 7b).

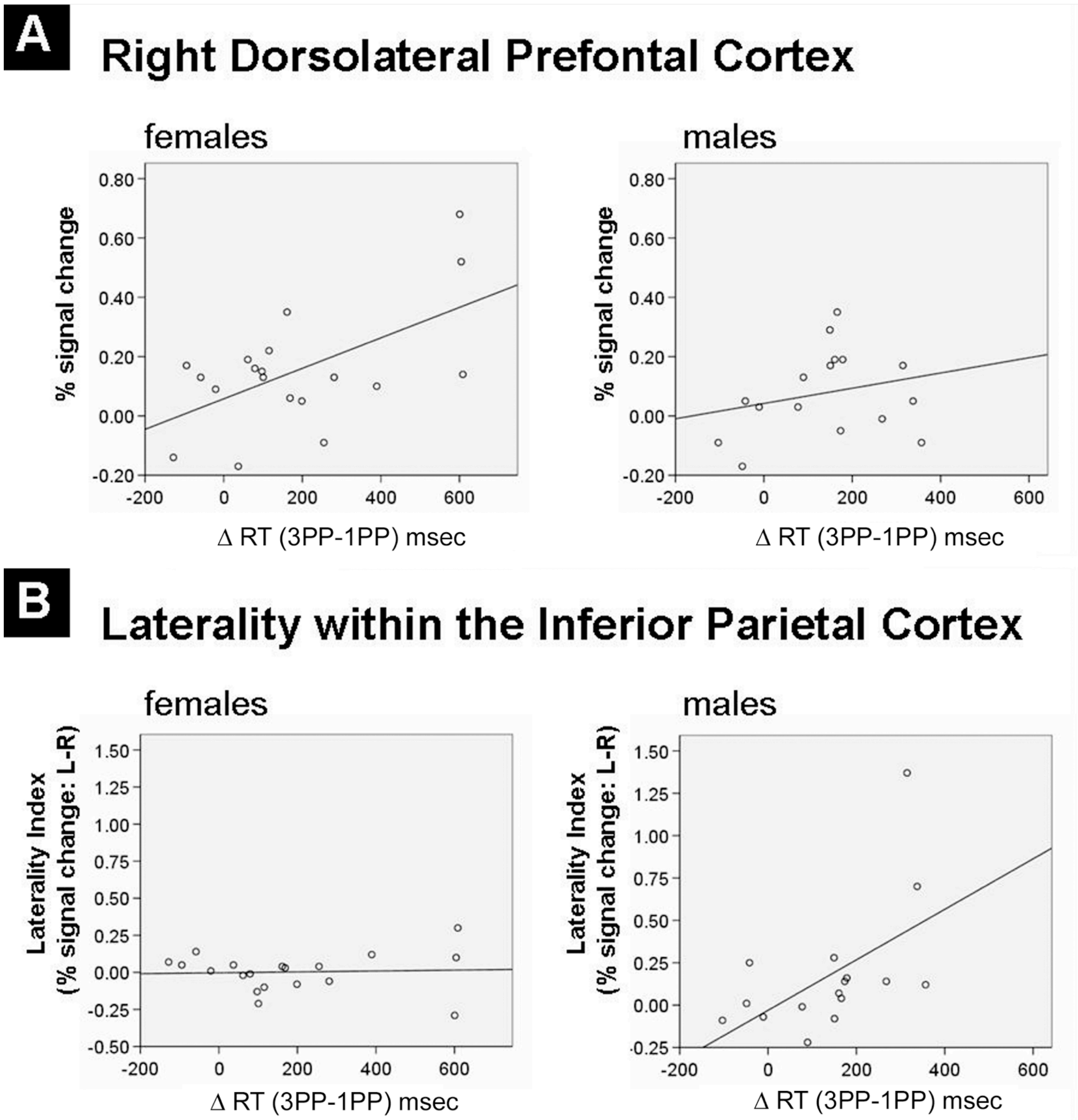

Figure 7A-B: A) This figure shows the regression analysis between △RT and percent signal change between 3PP and 1PP (△%signal change) within the ROI in the DLPFC for females and males. Significant regression analysis in females at *p*<0.01. B) This figure shows the regression analysis between △RT and lateralization (△%signal change between left and right inferior parietal cortex) for females and males. Significant regression analysis in males at *p*=0.05.

6.5. Discussion

This is the first study to compare the neural development of the ability to reason about other persons' mind between boys and girls. The objective of this study was to investigate the neural development of perspective taking by comparing brain activation in children, adolescents and adults, while they reasoned about another person's mind (3PP) versus their own preference (1PP).

Our data indicate that children, young adolescents and adults did not differ in appreciating Paul's preferences. Despite of the equivalent qualitative performance, we quantitatively found gender and age-group differences in the reaction times for 3PP versus 1PP judgments. Moreover, when we recorded brain activities with fMRI, we observed differences in the activated neuronal networks underlying perspective taking between males and females as well as between age groups. Processing 3PP activated predominantly the previously described frontal-parietal network across children, adolescents and adults (table 1). But our data show a different developmental pattern for boys and girls. More specifically, in females the development of the functional network was characterized by a decrease of activity in the right DLPFC, whereas it was related to changes in laterality within the inferior parietal cortex in males.

Dorsolateral prefrontal cortex

Only females activated the DLPFC during perspective taking and it seems that its specific role becomes less important with age. Although from behavioral studies there is no strong evidence that perspective-taking abilities develop beyond childhood, developmental-neuroimaging studies on social cognition in adolescents have shown that brain activity during social cognitive tasks continues to change during adolescence. Even though there are few studies on the development of the neural network underlying social cognitive processes, there seems to be some consistency regarding activity in the prefrontal cortex. Most of them reported a decrease in frontal brain activity with increasing age. Using a similar task, Pfeiffer et al. (Pfeifer et al., 2007) found the medial prefrontal cortex (mPFC) and the anterior cingulate cortex more activated in children than in adults during the adoption of a familiar other person's perspective (Harry Potter). Another neuroimaging-study found that the mPFC was more active in adolescents than in adults while participants were thinking about their own intention compared to thinking about physical causality (Blakemore et al., 2007). Because both of these studies focused on self-related processing comparison with our results is limited. Wang and colleagues investigated the development of the ability to understand irony. Understanding irony requires separating the literal meaning of a comment from its intended meaning. Again, children and adolescents activated the mPFC and the left inferior frontal gyrus more than adults (Wang et al., 2006). Compared to these findings a recent study found a decrease of prefrontal cortex activation within the dorsolateral prefrontal cortex (DLPFC) with increasing age (Dosch, 2009). The present findings seem to be in line with these finding in term of the decrease in DLPFC activation. While none of the reported studies investigated developmental gender-differences in brain activation underlying social cognitive tasks we observed a decrease of activation within the DLPFC which was restricted to females.

Inferior parietal cortex

To date little is known about developmental changes in the parietal cortex, particularly the inferior parietal cortex, which has been associated with processes related to social cognition in general and has been specifically implicated either during the processing of another person's perspective relative to one's own perspective (David et al., 2006; Jackson, Brunet et al., 2006; Ruby et al., 2001b; Ruby & Decety, 2003, 2004; Samson et al., 2004; Vogeley et al., 2001) or during imitation of another person's actions (Decety et al., 2003).

We found gender differences in the lateralization of brain activity between the left and the right parietal cortex. Whereas adults and boys as well as male adolescents showed left-lateralized IPC brain activation during perspective taking, girls and even more pronouncedly female adolescents showed bilateral IPC activation during 3PP judgments. It seems, therefore, that the inferior parietal cortex in the right hemisphere plays an important role in the development of the neural network fundamental to perspective taking and that it is differently involved in boys and girls. Gender differences in functional cerebral asymmetry are controversy discussed. A meta-analysis of imaging studies focusing on gender differences in lateralization quantifies gender differences as relatively small to not existent (Sommer et al., 2004) but most of the reported studies did not control the menstrual cycle phase in women and/or the underlying sex hormones. In a recent study investigating the role of sex hormones in language lateralization during the menstrual cycle could show dynamical and estrogen dependent differences in functional brain organization between the sexes (Weis et al., 2008). These findings may not be specific for language processing but might describe a more general mechanism of hormones mediated changes in functional brain organization. In consideration of these findings, the bilateral activation of the inferior parietal cortex during perspective-taking in girls and even more pronouncedly in female adolescents might be related to hormonal changes during development, especially since bilateral activation seems to be temporarily present and predominantly restricted to females.

General discussion

Whereas no emphasis was placed on speeded responses in the present task the data indicate that female and male were slower for 3PP than for 1PP in all age groups, except for female adolescents who were equally fast for 3PP and 1PP (Figure 6a).

Three earlier behavioural studies found a transient change in performance in face recognition. Whereas performance improved constantly during the first decade of life (decrease in RT), it was followed by a decline in performance (rise in RT) at the onset of puberty, which in girls was around the age of 10-11 years and in boys 11-12 years. Performance then improved again to the pre-puberty level (Blakemore, 2008; Carey et al., 1980; Diamond et al., 1983; Mcgivern et al., 2002). In a recent study the development of perspective-taking in adolescents was investigated using a task in which participants had to answer questions related to various scenarios from their own and from a protagonist's perspective (Choudhury et al., 2006). The data showed that reaction time differences between 3PP and 1PP were significantly greater in pre-adolescents but still existent in adolescents and adults, which is similar to our findings. In contrast to our results, however, Choudhury did not report any developmental gender differences. They concluded that decreasing △RT with development represents increasing efficiency in perspective-taking. In the current study we found a transient change in performance which indicated that female adolescents showed the best performance in processing another person's perspective since they did not need more time for 3PP than for 1PP judgments. While none of the mentioned studies investigated the neural bases of the reported increasing proficiency we were able to show that decreasing △RT was differently related to neural activity in males and females. In females, shorter △RT was related with less activation in the DLPFC and in males with a smaller degree of lateralization of the parietal cortex activation. Assuming that shorter △RT represents higher proficiency of perspective-taking (Choudhury, 2006), we conclude the more efficient females are, the less they need frontal regions, whereas the more efficient males are, the more they recruit the inferior parietal cortex of both hemispheres.

One might argue that changes in brain activation patterns could reflect simple performance differences instead of maturation as children almost always perform worse than adults on higher cognitive tasks. Since the task in this study was especially designed not to provoke performance differences (we showed that the participant's judgments for Paul were appropriate in all age-groups), we conclude that the differences most probably reflect maturation and not simple differences in performance. The fact that we did not find any gender differences in adults related either to behavior or to neuronal activation speaks for developmental changes in gender differences rather than permanent differences between men and women. Further, it could be argued that female participants required differential neuronal strategies for thinking about a male person, since only female subjects had to perform cross-gender judgments. We therefore asked children and adolescents to indicate how much they feel like Paul (irrespective of gender); we did not find a difference between girls and boys. This is further supported by the fact that general reaction times and judgments for 1PP and 3PP did not differ between females and males.

A principal weakness of this and other studies investigating social-information processing in adolescents is the lack of information about the developmental stages of puberty. A recent study investigating the interrelation between the pubertal rises in testosterone and estradiol and brain structure in 10-15 years old boys and girls demonstrated that the increased production of estradiol in pubescent girls seems to be directly related to the gray matter density decrease in frontal and parietal regions. Despite the described structural changes in neuroanatomy (Giedd et al., 1999; Gogtay et al., 2004; Sowell et al., 2004) many changes in social behavior take place during adolescence. Sexuality and romantic interest emerge; adolescents spend more time with peers than with their parents and families and the importance and complexity of peer relationships increases. A second weakness of the present study is the unbalance of female and male participants within the adult participants. Thus, there is a certain danger that the lack of gender differences in adults could be explained by the fact that eight of twelve participants were females.

The purpose of developmental neuroimaging studies is to gain insight into structural and functional maturation and the mechanism underlying basic developmental processes. It is very challenging to discern the effects of structural and hormonal variances, the brain's inherent plasticity and the dynamic interplay between the brain and its environment, especially during the time period of puberty. Our functional neuroimaging data showed that increasing proficiency in perspective taking has different neural underpinnings in girls and boys. In females it was related to decreasing activation in prefrontal cortex, whereas males showed decreased lateralization in the inferior parietal cortex

Growing comprehension of how changes in social behaviour, including social perception, social emotion and social cognition, are related to neurodevelopment and endocrinological variance will help to understand the brain-behavior relation in both normal and pathological conditions and, finally, will help to treat disorders involving impaired social behavior.

7 General Discussion

In the present PhD thesis the functional development of neuronal correlates of cognitive perspective taking was investigated. The first study describes the neural development of cognitive perspective taking in children and the second explored gender-related functional development of cognitive perspective taking in pubescent boys and girls.

The results of study 1 indicate that cognitive perspective taking develops after the age in which most classic social cognitive tasks are accomplishable. Although children and adults were equally appropriate in their judgments for another person, we found differences in the efficiency of perspective taking. In line with our findings Choudhury recently reported increasing proficiency in perspective taking during adolescence which she hypothesized might be related to the parallel development of its underlying neural circuitry (Choudhury et al., 2006). We showed for the first time that the development of perspective taking is associated with changes in brain activity within the described fronto-parietal network. Our results indicate a developmental shift from prefrontal to posterior and from bilateral to unilateral inferior parietal cortex brain activation. Even though there are only a few studies on the development of the neural network underlying social cognitive processes, several authors reported a decrease of medial prefrontal activation with age. Thus, the findings of the first study are in line with the previous developmental studies in terms of the decrease of prefrontal cortex activation. However, in contrast to the reported findings we mainly observed a decrease of activation within the dorsolateral prefrontal cortex instead of the medial prefrontal cortex. The DLPFC is known to play a critical role in executive function, particularly in cognitive control (Aron et al., 2004; Blasi et al., 2006; Bunge et al., 2002; Fecteau et al., 2007; Knoch et al., 2007; Knoch et al., 2006; Menon et al., 2001). From developmental psychology we know that higher cognitive control and attention functions develop long into adolescence (Davidson et al. 2006). Interestingly several social psychological studies have demonstrated that even adults frequently use self-knowledge as the primary basis for developing a model of what others know and feel, which has been described as a default mode of reasoning about others' mind. This egocentric bias can be interpreted as failure to suppress one's own perspective (Gilovich et al., 2002; Nickerson, 1999; Royzman et al., 2003; Vorauer et al., 1999). Considering this background the 3PP specific activation of the DLPFC in children may indicate that processing a 3PP requires children more than adults to inhibit their own prepotent egocentric perspective while they reason about Paul's perspective.

In addition our data provide new evidence that especially the parietal cortex plays an important role in the development of processing a third person's perspective. In contrast we did not find any developmental differences in brain activation associated with self-related processing.

As mentioned in the introduction, several functional neuroimaging studies indicated that the inferior parietal cortex particularly in the right hemisphere (including the temporo-parietal junction) is associated with a variety of social cognitive tasks such as perspective taking (e.g. (Ruby & Decety, 2003), theory of mind (Saxe et al., 2005) and empathy (Jackson, Brunet et al., 2006). This led to the speculation that this region is specialized for the human ability to reason about others affective and cognitive mental states (Saxe, 2006). However, it is important to note that the inferior parietal cortex is not only activated during higher-order social cognitive processes such as perspective taking but also when individuals are required to distinguish between themselves and others (Decety & Sommerville, 2003). Two recent studies demonstrated a selective impairment of self-other distinctions when repetitive transcranial magnetic stimulation (TMS) was applied over the right inferior parietal lobule as participants performed a perceptual task involving discrimination between photographs of themselves and of a familiar face (Uddin et al., 2006). Self-other judgments on whole arm reaching movements (Preston et al., 2008) were also impaired when TMS was applied over the right but not over the left inferior parietal cortex. These results provide direct evidence for a causal role of the right inferior parietal cortex for self-other discriminations. Furthermore, damage to this region not only led to the inability to represent other persons' perspective (Samson, 2004) it can also produce disorders associated with self-awareness, such anosognosia (Berlucchi et al., 1997). Direct electrical stimulation can induce out-of body experiences (i.e. the experience that oneself is located outside of the own body) (Blanke et al., 2002). In line with these findings, the additional activation of the right IPL during 3PP processing in children of our study might reflect that children compared to adults need more self-other discrimination during the processing of other people's perspectives. Since we were able to show that the activation of the right inferior parietal cortex was focal rather than diffuse, we suggest that the higher dependence on this brain region indicate that children use a different cognitive strategy. It seems that they need to keep the self-other distinction activated while they are anticipating another person's perspective.

Previous neuroimaging studies on development, reported similar patterns of neural activation among children and adults, whilst children convey more distributed patterns of neural activation and a decrease of BOLD signal as compared to adults. Such a change in patterns of neural activity has been referred to as a focalization of neural development (Casey et al., 2005; Durston et al., 2006). The usual explanation for greater variation in neural activity across brain regions is that cognitive strategies are less efficient in children, whereas enhanced activity in focal brain areas during maturation has been interpreted as being due to increased efficiency and neural pruning. A problem, however, with interpreting focalization in brain imaging is that differences in neural activity can be confounded by differences in variability between groups: a more heterogeneous or incoherent pattern of neural activity not only leads to a more distributed network but also to a reduction of neural activity. Thus, to determine if focalization of neural activity during maturation occurs, one has to disentangle measures of variance and measures of signal change (Berl et al., 2006; Xiong et al., 2000).

We found similar (or even reduced) degree of variance in the distribution of neural activity in children as compared with adults. Since the more widespread activation in children in our study can't be explained by greater inter-subject variances (neither within the adult network nor between different areas of the children's network) we conclude that children use a qualitatively different (extended) but a coherent rather than diffuse neural network.

A possible explanation for the differences in brain activation in children compared to adults is cortical maturation, in particular grey matter reorganization and white matter increase throughout adolescence and early adulthood. Since the prefrontal cortex and the inferior parietal cortex are among the last brain regions to mature (Gogtay et al., 2004) it is plausible that these region contains less well functioning connections, leading to more activation for tasks that recruit them. Alternatively one can argue that more attention is needed by children to perform the task (judge according to Paul). By separating the groups into good and bad performer we examined whether the differences in brain activation between children and adults are caused by maturation rather than performance differences in reaction times. Since we did not find performance related differences in brain activation we can rule out this argument.

The focus of the second study was the investigation of neural network underlying cognitive perspective taking at the onset of puberty. We were particularly interested in developmental differences between girls and boys. Although a handful studies explored developmental gender-differences in neural network until now nothing is known about gender-dependent development in perspective taking abilities. The results of the second study showed, that children, young adolescents and adults did not differ in their qualitative appreciation of a third-person's perspective and thus all participants performed the task appropriately. Despite the appropriate judgments, the results of the second study showed that the efficiency of perspective taking continues to develop during adolescence and in addition the development was different between girls and boys. Whereas the proficiency in females increases from the age of 8 to 14 years, this was much less the case for developing males. Furthermore, the developmental differences in the neural bases of perspective taking were especially pronounced during adolescent and different in girls and boys.

The results of study 1 revealed that children compared to adults showed more prefrontal and bilateral parietal activation patterns. We found any gender differences neither behavioral nor neuronal. In contrast to these finding, study 2 demonstrated that pubescent girls and boy significantly differ in their proficiency of perspective taking ($\triangle$RT) as well as in their neural activation patterns. We therefore analyzed how the efficiency is related to brain activation in females and males separately. These data indicated that the more efficient female children and adolescents are (lesser $\triangle$RT between 3PP and 1PP) the lesser their judgments were related to prefrontal brain activation. This was not the case for male children and adolescents. In males a lesser lateralization of activity within the inferior parietal cortex was found to be related with increasing proficiency in processing 3PP.

Importantly, the fact that gender-differences were not observable in children (8-10) and also absent in adults (whether behaviorally nor neuronal) suggests a different neural development between boys and girls rather than permanent differences between men and women. A transient shift of performance in social information processing has been described in earlier behavioral studies. The performance in face processing was found to increase during the first decade of life and was followed by a transient decline of performance during puberty after which performance again improved to the level before puberty (Blakemore, 2008; Blakemore et al., 2006; Carey et al., 1980; Diamond et al., 1983; Mcgivern et al., 2002). Interestingly, the dip in performance seem to be related to the onset of puberty rather than age per se – since it was earlier in girls (around the age of 10-11 years) and than boys (11-12).

Although, in our study as well as the mentioned studies no measures of puberty was taken, our behavioral and neuronal data together with the reported finding from behavioral studies suggest that sex hormones may influence neuroanatomical changes within the frontal and parietal cortex which in turn may influence the underlying cognitive processes during adolescence. Nevertheless, the present findings demonstrated that the neural network of perspective taking develops beyond childhood. The developmental changes are especially pronounced during puberty where females and males differ in their behavioral as well as neural development of cognitive perspective taking. But despite the reported development of cognitive perspective taking, many changes in social behavior take place during adolescence. Thus, to understand adolescent behavior more information about the interplay between socio-cultural factors, biological changes and social information-processing during puberty should be taking into account.

8. Outlook

While several studies investigated the neural development of social perception such as face recognition, only a handful studies focused on the development of the more complex social-cognitive information processing in the field of neuroscience as well as in developmental psychology (for review see Blakemore, 2008).

The investigation of the neural bases of social cognition requires the fragmentation of a complex ability into its components. Thus, real life situation are always much more complex than fMRI tasks can ever be. Therefore, for future research it might be useful to have instruments with naturalistic settings to assess children's and adolescent's social behavior outside the scanner environment which in turn can be compared with the neuronal development.

Studying the interplay between brain and social behavior during development is fascinating, but it poses also unique challenges. Beyond the lack of reliable tools to behaviorally asses social cognitive abilities there are many fundamental outstanding questions of general brain development.

How do structural, functional and cognitive development interact?

A very important question is, how synaptic reorganization influences neural activity and cognitive functions. Several developmental studies reported more widespread brain activation patterns in children compared to adults. The reported shift from diffuse to focal brain activation is presumably an experience-driven refinement of the association cortex. These findings seem to parallel changes observed over shorter time periods in studies of adult learning. There might be several alternative explanations for more extended brain activation. As children almost always perform worse than adults on higher cognitive tasks, the additionally activated brain regions might be a result of compensatory strategies. Furthermore, cognitive strategies to solve a specific task are likely to change with development – thus the degree of engagement of certain regions may systematically change with development.

Future work is needed to understand how learning during development affects activation pattern.

How to deal with enhances variability within developmental samples?

Another problem concerns the comparison of children's and adults activation pattern. Since children of the same age are likely to differ more than adults of the same age the statistical group comparison assumption that individual groups are homogenous is misleading – concerning structural features (grey and whiter matter) as well as performances level. Current fMRI analyses are designed to identify common brain activation within a population and thereby underestimate the contribution of individual activation patterns. Since the enhanced variability is a crucial characteristic of development, it is necessary to develop new methods to accurately identify normal and as well as adaptive or atypical variants of development.

What about the contribution of hormones?

Furthermore, virtually nothing is known about how neural activity and cognitive functions are affected by hormonal changes during adolescence. For a first step toward a better understanding of its relationship, it would be very helpful, when future studies could include measures of puberty (e.g. Tanner stages as well as hormone levels).

Taken together, late childhood and adolescence is a period of synaptic reorganization therefore, it might be argued that the brain is much more sensitive to social experiential inputs during this period of time. The present PhD thesis focused on the development of the neural bases and provided new evidence that cognitive perspective taking abilities develop beyond the age at which most classic social cognitive tasks are accomplishable. Furthermore we could show that pubescent girls and boys differ in their development. A comprehensive understanding of changes in children's and adolescents social behavior requires a multidisciplinary approach that recognizes the complex interactions between genetics, brain structures, physiology and chemistry as well as environment including socio-cultural influences.

Hopefully, social neuroscientist will keep collaborating with investigators from multiple disciplines such anthropology, ethnology, psychology as well as neurobiology, chemistry and endocrinology.

9. References

Aron, A.R., Robbins, T.W., & Poldrack, R.A. (2004). Inhibition and the right inferior frontal cortex. *TRENDS in Cognitive Sciences, 8*(4), 170-177.

Astington, J.W. (1993). *The child's discovery of the mind*. Cambridge, MA: Harvard University Press.

Baron-Cohen, S., Jolliffe, T., Mortimore, C., & Robertson, M. (1997). Another advanced test of theory of mind: evidence from very high functioning adults with autism or asperger syndrome. *J Child Psychol Psychiatry, 38*(7), 813-22.

Baron-Cohen, S., Leslie, A.M., & Frith, U. (1985). Does the autistic child have a "theory of mind"? *Cognition, 21*(1), 37-46.

Berlucchi, G., & Aglioti, S. (1997). The body in the brain: neural bases of corporeal awareness. *Trends in neurosciences, 20*(12), 560-4.

Berl, M.M., Vaidya, C.J., & Gaillard, W.D. (2006). Functional imaging of developmental and adaptive changes in neurocognition. Neuroimage, 30(3), 679-91.

Blakemore, S.J., & Choudhury, S. (2006). Development of the adolescent brain: implications for executive function and social cognition. *J Child Psychol Psychiatry, 47*(3-4), 296-312.

Blakemore, S.J. (2008). The social brain in adolescence. *Nature Review Neuroscience, 9*(4), 267-77.

Blakemore, S.J., den Ouden, H., Choudhury, S., & Frith, C. (2007). Adolescent development of the neural circuitry for thinking about intentions. *Soc Cogn Affect Neurosci, 2*(2), 130-139.

Blanke, O., Ortigue, S., Landis, T., & Seeck, M. (2002). Stimulating illusory own-body perceptions. *Nature, 419*(6904), 269-70.

Blasi, G., Goldberg, T.E., Weickert, T., Das, S., Kohn, P., Zoltick, B., Bertolino, A., Callicott, J.H., Weinberger, D.R., & Mattay, V.S. (2006). Brain regions underlying response inhibition and interference monitoring and suppression. *European Journal of Neuroscience, 23*(6), 1658-1664.

Bunge, S.A., Dudukovic, N.M., Thomason, M.E., Vaidya, C.J., & Gabrieli, J.D. (2002). Immature frontal lobe contribution to cognitive control in children: evidence from fMRI. *Neuron, 33*, 301-311.

Buonomano, D.V., Menenich, M.M. (1998): Cortical plasticity: from synapses to maps. *Annual Review Neuroscience 21:* 149-86

Casey, B.J., Tottenham, N., Liston, C., & Durston, S. (2005). Imaging the developing brain: what have we learned about cognitive development? *Trends in Cognitive Science, 9*(3), 104-10.

Carey, S., Diamond, A., & Wood, W. (1980). The development of face recognition - a maturational component. *Developmental Psychology, 16*, 257-269.

Carpenter, M., Nagell, K., & Tomasello, M. (1998). Social cognition, joint attention, and communicative competence form 9 to 15 month of age. *Monographs of the Society for Research in Child Development, 63*, 1-143.

Casey, B.J., Galvan, A., & Hare, T.A. (2005). Changes in cerebral functional organization during cognitive development. *Curr Opin Neurobiol, 15*(2), 239-44.

Casey, B.J., Tottenham, N., Liston, C., & Durston, S. (2005). Imaging the developing brain: what have we learned about cognitive development? *Trends in Cognitive Science, 9*(3), 104-10.

Cavanna, A.E., & Trimble, M.R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain, 129*(Pt 3), 564-83.

Choudhury, S., Blakemore, S.J., & Charman, T. (2006). Social cognitive development during adolescence. *Social Cognitive and Affective Neuroscience, 3*, 165-174.
D'Argembeau, A., Ruby, P., Collette, F., Degueldre, C., Balteau, E., Luxen, A., Maquet, P., & Salmon, E. (2007). Distinct regions of the medial prefrontal cortex are associated with self-referential processing and perspective taking. *Journal of Cognitive Neuroscience, 19*(6), 935-44.
Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L.L., Parvizi, J., & Hichwa, R.D. (2000). Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nature Neuroscience, 3*, 1049–1056.
David, N., Bewernick, B.H., Cohen, M.X., Newen, A., Lux, S., Fink, G.R., Shah, N.J., & Vogeley, K. (2006). Neural representations of self versus other: visual-spatial perspective taking and agency in a virtual ball-tossing game. *Journal of Cognitive Neuroscience, 18*(6), 898-910.
Decety, J., Grezes, J., Costes, N., Perani, D., Jeannerod, M., Procyk, E., Grassi, F., & Fazio, F. (1997). Brain activity during observation of actions. Influence of action content and subject's strategy. *Brain, 120 (Pt 10)*, 1763-77.
Decety, J., & Jackson, P.L. (2004). The functional architecture of human empathy. *Behav Cogn Neurosci Rev, 3*(2), 71-100.
Decety, J., & Keenan, J.P. (2006). Social Neuroscience: A new journal. *Soc Neurosci, 1*(1), 1-4.
Decety, J., & Sommerville, J.A. (2003). Shared representations between self and other: a social cognitive
Decety, J., & Sommerville, J.A. (2003a). Shared representations between self and other: a social cognitive neuroscience view. *Trends in Cognitive Science, 7*(12), 527-33.
Diamond, A., Carey, S., & Back, K. (1983). Genetic influences on the development of spation skills during early adolescents. *Cognition, 13*, 167-185.
Dosch M., Loenneker T., Bucher K., Martin E., Klaver P. (2010). Learning to appreciate others: neural development of cognitive perspective taking. *Neuroimage*, 50(2): 837-46.
Durston, S., & Casey, B.J. (2006a). A shift from diffuse to focal cortical activity with development: the authors' reply. *Dev Sci, 9*(1), 18-20.
Durston, S., & Casey, B.J. (2006b). What have we learned about cognitive development from neuroimaging? *Neuropsychologia, 44*(11), 2149-57.
Durston, S., Davidson, M.C., Tottenham, N., Galvan, A., Spicer, J., Fossella, J.A., & Casey, B.J. (2006). A shift from diffuse to focal cortical activity with development. *Developmental Science, 9*(1), 1-8.
Elbert, T., Heim, S., & Rockstroh, B. (2001). Neural Plasticity and Development. In C. A. Nelson & M. Luciana (Eds.), *Handbook of Developmental Cognitive Neuroscience*. Cambridge, Massachusetts, London, England: MIT Press.
Fecteau, S., Knoch, D., Fregni, F., Sultani, N., Boggio, P., & Pascual-Leone, A. (2007). Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. *J Neurosci, 27*(46), 12500-5.
Flavell, J.H. (1992). Perspectives on perspective taking. In H. Beilin & P. Putfall (Eds.), *Piaget's Theory: Prospects and Possibility* (pp. 107-139). Hillsdale, NJ: Erlbaum.
Flavell, J.H. (1999). Cognitive development: children's knowledge about the mind. *Annual Review of Psychology, 50*, 21-45.
Fletcher, P.C., Happe, F., Frith, U., Baker, S.C., Dolan, R.J., Frackowiak, R.S., & Frith, C.D. (1995). Other minds in the brain: a functional imaging study of "theory of mind" in story comprehension. *Cognition, 57*(2), 109-28.
Frith, U., & Frith, C.D. (2003). Development and neurophysiology of mentalizing. *Philos Trans R Soc Lond B Biol Sci, 358*(1431), 459-73.

Gallagher, H.L., & Frith, C.D. (2003). Functional imaging of 'theory of mind'. *TRENDS in Cognitive Sciences, 7*(2), 77-83.
Gallese, V., & Goldmann, A. (1998). Mirror neurons and the simulation theory of mindreading. *Trends of Cognitive Science, 2*, 493-501.
Gallese, V., Keysers, C., & Rizzolatti, G. (2004). A unifying view of the basis of social cognition. *Trends Cogn Sci, 8*(9), 396-403.
Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., Paus, T., Evans, A.C., & Rapoport, J.L. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nature Neuroscience*(2), 861–863.
Nature Neuroscience(2), 861–863.
Gilovich, t., Kruger, J., & Medvec, V.H. (2002). The spotlight effect revisited: Overestimating the manifest variability of our actions and appearance. *Journal of Experimental Social Psychology, 38*, 93-99.
Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., Nugent III., T.F., Herman, D.H., Clasen, L.S., Toga, A.W., Rapoport, J.L., & Thompson, P.M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America, 101*, 8174–8179.
Gopnik, A. (1993). How we know our minds: The illusion of first-person knowledge of intentionality. *Behavioral and Brain Science, 16*, 1-15, 90-101.
Gopnik, A., & Meltzoff, A.N. (1997). *Words, Thoughts, and Theories*. Cambridge, MA: MIT Press.

Gusnard, D.A., Raichle, M.E., & Raichle, M.E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nat Rev Neurosci, 2*(10), 685-94.
Harris, P. (1995). From simulation to folk psychology: the case for development. In M. Davies & T. Stone (Eds.), *Folk Psychology* (pp. 207-231). Oxford: Blackwell Publishers.
Hebb, O.D. (1949). *The organization of behavior: A neurophyiological theory*. New York: Wiley.

Huttenlocher, P.R. (1990). Morphometric study of human cerebral cortex development. *Neuropsychologia, 28*,
Jackson, P.L., Brunet, E., Meltzoff, A.N., & Decety, J. (2006). Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain. *Neuropsychologia, 44*(5), 752-61.
Jackson, P.L., Meltzoff, A.N., & Decety, J. (2006). Neural circuits involved in imitation and perspective-taking. *Neuroimage, 31*(1), 429-39.
Johnson, S.C. (2003). Detecting agents. *Journal of Philosophical Transactions of the Royal Society of London, Biological Science* (358), 549-59.
Knoch, D., & Fehr, E. (2007). Resisting the power of temptations: the right prefrontal cortex and self-control. *Ann N Y Acad Sci, 1104*, 123-34.
Knoch, D., Gianotti, L., R., Pascual-Leone, A., Treyer, V., Regard, M., Hohmann, M., & Brugger, P. (2006). Disruption of right prefrontal cortex by low-frequency repetitive transcranial magnetic stimulation induces risk-taking behavior. *Journal Neuroscience, 26*(24), 6469-6472.
Keysers, C., Wicker, B., Gazzola, V., Anton, J.L., Fogassi, L., & Gallese, V. (2004). A touching sight: SII/PV activation during the observation and experience of touch. *Neuron, 42*(2), 335-46.
Lamm, C., Batson, C.D., & Decety, J. (2007). The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. *Journal of Cognitive Neuroscience, 19*(1), 42-58.

Larson, R.W. (2001). How U.S. Children and Adolescents Spend Time: What It Does (and Doesn't)Tell Us About Their Development. *Current Directions in Psychological Science, 10*(5), 160-164.

Lundstrom, B.N., Ingvar, M., & Petersson, K.M. (2005). The role of precuneus and left inferior frontal cortex during source memory episodic retrieval. *Neuroimage, 27*, 824-834.

Preston, C., & Newport, R. (2008). Misattribution of movement agency following right parietal TMS. Social Cognitive and Affective Neuroscience, 3, 26-32.

McGivern, R.F., Andersen, J., Byrd, D., Mutter, K.L., & Reilly, J. (2002). Cognitive efficiency on a match to sample task decreases at the onset of puberty in children. Brain and Cognition, 50, 73-89.

Mesulam, M.M. (1981). A cortical network for directed attention and unilateral neglect. *Annals of Neurology,*

Menon, V., Adleman, N.E., White, C.D., Glover, G.H., & Reiss, A.L. (2001). Error-related brain activation during a go/nogo response inhibition task. *Human Brain Mapping, 12*, 131-143.

Mesulam, M.M. (1981). A cortical network for directed attention and unilateral neglect. *Annals of Neurology, 10*(4), 309-325.

Mitchell, J.P., Macrae, C.N., & Banaji, M.R. (2006). Dissociable medial prefrontal contributions to judgments of similar and dissimilar others. *Neuron, 50*(4), 655-63.

Neufang, S., Specht, K., Hausmann, M., Gunturkun, O., Herpertz-Dahlmann, B., Fink, G.R., & Konrad, K. (2009). Sex differences and the impact of steroid hormones on the developing human brain. *Cerebral Cortex, 19*(2), 464-73.

Nickerson, R.S. (1999). How we know-and sometimes misjudge-what we know: Imputing one's own knowledge to others. *Psychological Bulletin, 126*, 747-753.

Oldfield, R. (1971). The Assessment and Analysis of Handedness: The Edinburgh Inventory. *Neuropsychologia* (9), 97-113.

Olsson, A., & Ochsner, K.N. (2008). The role of social cognition in emotion. *Trends in Cognitive Science, 12*(2), 65-71.

Paus, T. (2005). Mapping brain maturation and cognitive development during adolescence. Trends Cogn Sci,

Peper J.S., Brouwer R.M., Schnack H.G., van Baal G.C., van Leeuwen M., van den Berg S.M., Delemarre-Van de Waal H.A., Boomsma D.I., Kahn R.S., Hulshoff Pol H.E. (2009). Sex steroids and brain structure in pubertal boys and girls. *Psychoneuroendocrinology*, 34(3), 332-42.

Piaget, J. (1959). *Judgment and reasoning in the child*: Littlefield, Adams, & Co, Paterson.

Pfeifer, J.H., Lieberman, M.D., & Depretto, M. (2007). I know you are but what am I?!: neural bases of self- and social knowledge retrieval in children and adults. *Journal of Cognitive Neuroscience, 19*, 1323-1337.

Piefke, M., Weiss, P.H., Zilles, K., Markowitsch, H.J., & Fink, G.R. (2003). Differential remoteness and emotional tone modulate the neural correlates of autobiographical memory. *Brain, 126*, 650-668.

Premack, D., & Woodruff, g. (1978). Does the chimpanze have a theory of mind? Behavioral Brain Science, 1,

Preston, C., & Newport, R. (2008). Misattribution of movement agency following right parietal TMS. *Social Cognitive and Affective Neuroscience, 3*, 26-32.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., & Shulman, G.L. (2001). A default mode of brain function. Proc Natl Acad Sci U S A, 98(2), 676-82.

Royzman, E.B., Baron, J., & Wright Cassidy, K. (2003). "I know, You Know": Epistemic Egocentrism in Children and Adults. *Review of General Psychology, 7*(1), 38-65.

Ruby, P., & Decety, J. (2001). Effect of subjective perspective taking during simulation of action: a PET investigation of agency. *Nature Neuroscience, 4*(5), 546-50.

Ruby, P., & Decety, J. (2003). What you believe versus what you think they believe: a neuroimaging study of conceptual perspective-taking. *European Journal of Neuroscience, 17*(11), 2475-80.
Ruby, P., & Decety, J. (2004). How would you feel versus how do you think she would feel? A neuroimaging study of perspective-taking with social emotions. *Journal of Cognitive Neuroscience, 16*(6), 988-99.
Samson, D., Apperly, I.A., Chiavarino, C., & Humphreys, G.W. (2004). Left temporoparietal junction is necessary for representing someone else's belief. *Nature Neuroscience, 7*(5), 252-264.
Saxe, R. (2006). Uniquely human social cognition. *Current Opinion in Neurobiology, 16*(2), 235-9.
Saxe, R., & Wexler, A. (2005). Making sense of another mind: the role of the right temporoparietal junction. *Neuropsychologia, 43*(10), 1391-9.
Schilbach, L., Eickhoff, S.B., Rotarska-Jagiela, A., Fink, G.R., & Vogeley, K. (2008). Minds at rest? Social cognition as the default mode of cognizing and its putative relationship to the "default system" of the brain. *Conscious Cogn, 17*(2), 457-67.
Singer, T., Seymour, B., O'Doherty, J.P., Stephan, K.E., Dolan, R.J., & Frith, C.D. (2006). Empathic neural responses are modulated by the perceived fairness of others. *Nature, 439*(7075), 466-9.
Sommer, I.E., Aleman, A., Bouma, A., & Kahn, R.S. (2004). Do women really have more bilateral language representation than men? A meta-analysis of functional imaging studies. *Brain, 127*(Pt 8), 1845-52.
Sowell, E.R., Peterson, B.S., Thompson, P.M., Welcome, S.E., Henkenius, A.L., & Toga, A.W. (2003). Mapping cortical change across the human life span. *Nat Neurosci, 6*(3), 309-15.
Sowell, E.R., Thompson, P.M., Leonard, C.M., Welcome, S.E., Kan, E., & Toga, A.W. (2004). Longitudinal mapping of cortical thickness and brain growth in normal children. *J Neurosci, 24*(38), 8223-31.
Sowell, E.R., Thompson, P.M., Peterson, B.S., Mattson, S.N., Welcome, S.E., Henkenius, A.L., Riley, E.P., Jernigan, T.L., & Toga, A.W. (2002). Mapping cortical gray matter asymmetry patterns in adolescents with heavy prenatal alcohol exposure. *Neuroimage, 17*(4), 1807-19.
Spelke, E.S., Phillips, A.T., & Wooward, A.L. (1995). Infants' knowledge of object motion and human action. In D. Sperber, D. Premack & A. Premack (Eds.), *Causal cogntion: A multidisciplinary debate*. Oxford, UK: Oxford University Press.
Taylor, M., Esbensen, B.M., & Bennett, R.T. (1994). Children's understanding of knowledge acquisition: the tendency for children to report that they have always known what they have just learned. *Child Development, 65*(6), 1581-604.
Toga, A.W., Thompson, P.M., & Sowell, E.R. (2006). Mapping brain maturation. *Trends in neurosciences, 29*(3), 148-59.
Uddin, L.Q., Molnar-Szakacs, I., Zaidel, E., & Iacoboni, M. (2006). rTMS to the right inferior parietal lobule disrupts self-other discrimination. *Soc Cogn Affect Neurosci, 1*(1), 65-71.
Uttal, W.R.C., & Press., M.M. (2003). *The new phrenology: The limits of localizing cognitive processes in the brain*: MA: MIT Press.
Vogeley, K., Bussfeld, P., Newen, A., Herrmann, S., Happe, F., Falkai, P., Maier, W., Shah, N.J., Fink, G.R., & Zilles, K. (2001). Mind reading: neural mechanisms of theory of mind and self-perspective. *Neuroimage, 14*(1 Pt 1), 170-81.
Vogeley, K., May, M., Ritzl, A., Falkai, P., Zilles, K., & Fink, G.R. (2004). Neural correlates of first-person perspective as one constituent of human self-consciousness. *Journal of Cognitive Neuroscience, 16*(5), 817-27.

Vorauer, J.D., & Ross, M. (1999). Self-awareness and feeling transparent: Failing to suppress one's self. *Journal of Experimental Social Psychology, 35*, 415-440.

Wang, A.T., Lee, S.S., Sigman, M., & Dapretto, M. (2006). Neural basis of irony comprehension in children with autism: the role of prosody and context. *Brain, 129*(Pt 4), 932-43.

Wang, A.T., Lee, S.S., Sigman, M., & Dapretto, M. (2007). Reading affect in the face and voice: neural correlates of interpreting communicative intent in children and adolescents with autism spectrum disorders. *Arch Gen Psychiatry, 64*(6), 698-708.

Weis, S., Hausmann, M., Stoffers, B., Vohn, R., Kellermann, T., & Sturm, W. (2008). Estradiol modulates functional brain organization during the menstrual cycle: an analysis of interhemispheric inhibition. *J Neurosci, 28*(50), 13401-10.

Wicker, B., Keysers, C., Plailly, J., Royet, J.P., Gallese, V., & Rizzolatti, G. (2003). Both of us disgusted in My insula: the common neural basis of seeing and feeling disgust. *Neuron, 40*(3), 655-64.

Wiesel, T.N., & Hubel, D.H. (1963). Single-Cell Response in Striate Cortex of Kittens Deprived of Vision in One Eye. *Journal of Neurophysiology, 26*, 1003-1017.

Wilke, M., Krageloh-Mann, I., & Holland, S.K. (2007). Global and local development of gray and white matter volume in normal children and adolescents. *Exp Brain Res, 178*(3), 296-307.

Wimmer, H., & Perner, J. (1983). Beliefs about beliefs: Representation and constraining function of wrong beliefs in young children's understanding of deception. *Cognition, 13*, 103-128.

Xiong, J., Rao, S., Jerabek, P., Zamarripa, F., Woldorff, M., Lancaster, J., & Fox, P.T. (2000). Intersubject variability in cortical activations during a complex language task. *Neuroimage, 12*(3), 326-39.

C U R R I C U L U M   V I T A E

PERSONAL DATA

Name	Mengia Dosch
Address	Merkurstrasse 37 8032 Zürich Switzerland
Mobile:	+41 76 369 1909
Email:	mengiadosch@gmail.com

Citizen of:	Tinizong-Rona (GR)
Place of Birth:	Basel
Date of Birth:	19.08.1977
Martial Status	unmarried

EDUCATION AND QUALIFICATIONS

August, 2008	Doctoral examination: Learning to Appreciate Others: Neural Development of Adopting other People's Perspectives (Prof. E. Martin, Prof. L. Jäncke)
2005-2008	PhD student and scientific assistant at the MR Center, University Children's Hospital Zurich, Prof. E. Martin-Fiori.
2004-2005	Scientific assistant at the MR Center, University Children's Hospital Zurich, Prof. M. von Aster and Prof. E. Martin-Fiori
May, 2004	College graduation
1998-2004	Study of Psychology at the University of Bern, 1. Subsidiary Subject: socio-scientific research methods and statistics. 2. Subsidiary Subject: Psychopathology
2001-2002	Student exchange, Ludwig-Maximilian University, Munich, Germany
1998	High school graduation

PRACTICAL EXPERIENCE

2003	Internship, New York City University, Neuropsychology Department, New York
2002	Internship, Children's and Adolescent's Psychiatry, University Hospital of Bern

2001-2002	Internship, Max Plank Institute for Human Cognitive and Brain Science, Munich, Germany
2001	Internship, Neurological Clinic, Department of Neuropsychology, University Hospital Zurich
2001	Tutor, Department of Psychology, Developmental Psychology, University of Bern

PUBLICATIONS

Book chapter

Von Aster, M. & Dosch, M. Entwicklungsbezogene Rechenstörungen. In: Schule und psychische Störungen (Steinhausen, H.C., Ackermann, N., Hrg.) Stuttgart: Kohlhammer

Peer Reviewed Publications

Dosch, M., Loenneker T., Bucher, K, Martin, E, Klaver, P. (2010). Learning to appreciate others: Neural development of cognitive perspective taking. Neuroimage, 50(2):837-46

Dosch, M., Loenneker T., Bucher, K, Martin, E, Klaver, P. (2009). Adopting another person's mind: girls and boys neural development of cognitive perspective taking. Submitted to Social Cognitive an Affective Neuroscience

Kucian K., Loenneker T., Dietrich T., Dosch M., Martin M., von Aster M. Impaired Neural Networks for Number Processing in Dyscalculic Children (2006). Behavioral and Brain Functions, 5;2:31.

Invited presentations

Dosch, M. Entwicklung der kognitiven Perspektivenübernahme und ihre neuronalen Grundlagen. Fachtagung Autismus-Forschung, Autismus deutsche Schweiz, Zürich, November 2007

Dosch, M. Neural development of perspective taking in preadolescent children. 10th Congress of the Swiss Society of Psychology, Zurich, September 2007

Dosch, M. Einblick in die Theory of Mind Forschung. Fortbildung Abteilung Psychosomatik und Psychiatrie Kinderspital Zürich, August, 2006

Dosch, M. Regard, M. Parler avec soi-même. Tagung der Schweizerischen Gesellschaft für Verhaltensneurologie, Genf, September, 2003

Dosch, M. Das Selbstgespräch – eine neuropsychologische Studie. KLINEX (Kolloquium für Klinische und Experimentelle Neuropsychologie), Universitätsspital Zürich, Juni, 200

Posters

Dosch, M, Loenneker, T, Martin, E, Klaver, P. Neural development of cognitive perspective taking in school aged children (8-10 years). Cognitive Neuroscience Conference in San Francisco, 2008

Dosch, M, Loenneker, T, Martin, E, Klaver, P. Neural development of cognitive perspective taking. Symposium of the Neuroscience Center Zurich (ZNZ), 2007

Dosch M, Haker H, Rössler W, Martin E, Loenneker T. Mirror neuron activity in contagious yawning. Human Brain Mapping in Florence, 2006

Dosch M, Haker H, Rössler W, Martin E, Loenneker T. Mirror neuron activity in contagious yawning. Symposium of the Neuroscience Center Zurich (ZNZ), 2006

Dosch M, Kucian K, Loenneker T, von Aster M, Martin E, Dietrich T. Symposium of the Neuroscience Center Zurich (ZNZ), 2005

Dosch M, Kucian K, Loenneker T, von Aster M, Martin E, Dietrich T. Language laterality in children with developmental dyscalculia - a running fMRI study. Human Brain Mapping in Toronto, 2005